PHARMACEUTICAL INNOVATION—PROMISES AND PROBLEMS

HEARING

BEFORE THE

SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT

AND THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

OF THE

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PHARMACEUTICAL INNOVATION—PROMISES AND PROBLEMS

MONDAY, APRIL 27, 1981

HOUSE OF REPRESENTATIVES, COMMITTEE ON SCIENCE AND TECHNOLOGY, SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT; SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,

Washington, D.C.

The subcommittees met in joint hearing, pursuant to call, in room 2318, Rayburn House Office Building, commencing at 2:10 p.m., Hon. James H. Scheuer and Hon. Albert Gore, Jr., presiding.

Present: Representatives Scheuer, Gore, Carney, Walgren, Schneider, Walker, and White.

Mr. SCHEUER. The meeting of the Subcommittee on Natural Resources, Agriculture Research and Environment, jointly with the Oversight and Investigations Subcommittee, of the Committee on Science and Technology, will come to order.

It is a great pleasure for me to begin these hearings on the subject of pharmaceutical research jointly with the Oversight and Investigations Subcommittee. It has been a particular pleasure working with Congressman Al Gore, the chairman of the Oversight and Investigations Subcommittee, and he has added enormously to the development of these hearings through his high intelligence, his thoughtfulness, and his insights.

Pharmaceutical research, of course, holds the promise of dramatic health improvements, both for ourselves and for generations to come. This has been true over the years, and it's particularly true now. In past decades great innovations in drug research have been responsible for saving hundreds of thousands of lives, and for ending or easing the suffering and debilitating illnesses of millions of people.

Over the years we have come to expect great advances from our U.S.-based health and pharmaceutical industry. Indeed, we depend upon their continued success in research and development to preserve and protect the health and the very lives of our people.

So it is somewhat ironic and somewhat painful for me that, at a time when we're on the verge of controlling if not conquering many of the dreaded diseases of our day, we are confronted with a regulatory apparatus for drug approval that vastly adds to both the time and the cost of marketing new and innovative drugs with dramatic health-enhancing and life-saving potential. There is compelling evidence that unduly burdensome regulatory requirements,

coupled with unfair and inequitable tax laws, are slowing if not crippling, desperately needed new drug innovation.

Thousands of our fellow citizens are needlessly suffering and dying, when recently developed, dramatic new drugs could help save lives and enhance lives. I speak especially of the so-called compassionate investigational new drugs—IND's—and the orphan drugs which have been the subject of hearings by the Health and Environment Subcommittee of the Commerce Committee on which I also serve.

In an effort to alleviate the needless suffering of many thousands of our people, I have today introduced legislation, cosponsored by several of my colleagues, which if enacted will go a long way in reducing the regulatory obstacles which prevent Americans from getting the very best of health care.

Now, let me make it clear that the Federal Government has a necessary and proper and, indeed, an indispensible role in assuring that new drugs are both safe and effective. The purpose of my bill and the purpose of these hearings, and the purpose of our effort to speed up the regulatory process and the approval of new drugs, is to improve the risk benefit prospects of patients and not to weaken or destroy them. We are desperately eager to enhance the health prospects for Americans, not to lessen them.

Let me also point out that, apart from what we are doing here in Congress on Capitol Hill, I am very much encouraged by the clear signals from the administration that its commitment to reforming drug regulations is sound and solid.

Just before the congressional recess I met at the White House with Vice President George Bush, an old and valued colleague, and with Mr. James Miller, the Staff Director of the White House Task Force on Regulatory Reform. We discussed many of the shortcomings of the existing regulatory process. We discussed the need for improving the system of validating new drugs as well as the need for granting compassionate IND's, and for addressing the matter of orphan drugs. That meeting was very encouraging and I am pleased to say the administration seems committed to a long overdue revision of Federal procedures for regulating and approving innovative new drugs.

Today's hearings will focus on breakthrough drugs. Some of these have already been approved for use in the United States, while a number of other important ones still await final regulatory approval. We look forward with great pleasure to hearing from our distinguished panel of scientists today on what the latest advances in pharmacology promise us, and the kind of reforms and improvements in the regulatory and approval process of drugs which will speed the day when they're available for enhancing the health prospects and the quality of life for the 226 million American health consumers.

I now yield to my colleague, Congressman Al Gore, for a statement.

Mr. GORE. Thank you very much, Mr. Chairman.

I would like to commend you for your initiative in conducting this hearing, and for your persistence in demanding that the Food and Drug Administration carry out its mandate to protect the public in the most efficient possible way. I look forward to this

hearing as the first in a series of joint efforts to spotlight the strengths and deficiencies of the Federal drug approval process. I can think of no more propitious time to begin than with the inauguration of a new Commissioner of Food and Drugs. The message of this hearing—that the FDA needs to improve its new drug approval process—should be carried loudly and clearly to Dr. Hayes and to the new administration.

I am, and will continue to be, a strong proponent of the necessity to protect the public from harmful or ineffective drugs and food products. I am also committed to insuring that the public knows about the effects of these products and receives them at the least possible cost.

On infant formulas, contact lenses, the amount of salt in food, the approval of generic drugs, and on other issues, I have sometimes been critical of industry practices which are not in the best interests of the public health. And I will continue to encourage the administration and the industry on issues like patients' package inserts. And at the same time, I recognize that these industries, and particularly the pharmaceutical industry, are among our most innovative, most productive, and most valuable.

We must insure that potentially lifesaving new discoveries reach the market in the shortest possible time. The prevention and treatment of disease must go hand in hand; the American people deserve no less. There is no reason, why our Government cannot be efficient in dealing with drug applications, at the same time that it is effective in carrying out its health protection mandate.

In this context, I think that an examination of some potentially important advances in drug therapy is timely. Not only will we hear about the cutting edge of American science, but we will be able to take what we learn to the FDA and ask that some of those new discoveries be given priority treatment. FDA has already instituted some new procedures, and the agency needs to know that we will be following the progress of these drugs very closely.

But it is not enough merely to deal with drugs on a case-by-case basis. In the future, the Investigations and Oversight Subcommittee will be examining some important structural issues that affect research and development in the pharmaceutical industry. For example, we will want to examine whether the FDA relies too little on the advice of its scientific advisory committees in approving new drugs.

We will be interested in examining the alleged effects of generic drug development on industry research and development investments. We will want to see why the ratio of basic research to sales has not kept pace in the last decade. We will want to see whether FDA can make better use of data from validated foreign studies to conserve precious research dollars. We will want to examine the effects of cross licensing of drugs in other nations.

I know that the Health and Environment Subcommittee, chaired by my distinguished colleague, Mr. Waxman, has just completed hearings on the subject of patent term restoration, an issue of great interest to the pharmaceutical industry. I hope that this hearing, plus the additional ones I intend to conduct, some jointly with Chairman Sheuer, will give us a better picture of the problems that face both the industry and the FDA, so that we can de-

termine what is reasonable to expect from the approval process itself, and what needs to be settled by other means.

Thank you, Mr. Chairman.

Mr. SCHEUER. Thank you very much, Congressman Gore.

And now my distinguished ranking minority member, Congressman Bill Carney of New York.

Mr. CARNEY. Thank you, Mr. Chairman.

I would like to compliment both you and Mr. Gore for proposing these hearings, as the problems we will address today are real ones, indeed. Your leadership in addressing the difficulties of the medical community and the pharmaceutical industry in bringing vital new drugs to the marketplace represents a true public service, for only by bringing these problems to the attention of the public and the Congress can we expect to find solutions. You are to be commended for your continuing leadership on this matter.

I believe that changes are needed in the way the nation develops new drugs and approves them for public use, as the chairman has so aptly described in his statement. However, the problem regarding this aspect of regulation of the pharmaceutical industry is only one element of the overall regulatory morass we have allowed ourselves to develop in the United States. There are numerous instances where we have permitted too much regulation, and we are now paying the penalty. I personally support the regulatory reform efforts proposed by the Reagan administration, and believe that nowhere do they have as much potential for direct benefit to people as they do in the issue before us today.

I would note, too, that as far as this committee is concerned, although our primary interest is with the research, development, and demonstration that produces new drugs, new energy sources, and so on, we cannot be unconcerned, especially in the case of new pharmaceutical products, with impediments to bringing this research and development to fruition. If there is anything further that can be done in the front end—in the R. & D.—that can alleviate the regulatory problems that can be just as real as unsuccessful research in denying the benefits of a new drug to society, then we want to know about it. That is one of the points we hope the witnesses will address today.

Finally, I would like to say a word about another aspect of medical research that is of particular interest to me, and in which I see some of the same difficulties and frustrations in achieving its full potential as we do in the development of new drugs. I am speaking of the nuclear medicine program, which has been highly successful so far in being accepted as an everyday part of medical practice. I am informed that over 60 million nuclear medical procedures were conducted in the United States last year. We are now, however, faced with a situation where a shortage of R. & D. funds may hamper further progress, and the continued broadening of this technology to benefit additional patients. This is a subject that I believe this committee will speak to later, but I could not help drawing a parallel with the pharmaceutical development and use situation at this time.

Mr. Chairman, I again commend you for holding this hearing and I would like to say I commend you for the legislation you submitted today. I am proud to be a part of that legislation as a co-

sponsor. I would like to welcome our distinguished witnesses and I am looking forward to their testimony.

Mr. SCHEUER. Thank you very much, Congressman Carney.

Congressman Doug Walgren of Pennsylvania.

Mr. WALGREN. I have no statement, Mr. Chairman. Thank you.

Mr. SCHEUER. Thank you.

Congresswoman Claudine Schneider.

Mrs. SCHNEIDER. No, thank you, Mr. Chairman.

Mr. SCHEUER. Congressman Richard White of Texas.

Mr. WHITE. Thank you, Mr. Chairman. I am looking forward to the testimony.

Mr. SCHEUER. All right.

I am going to call on Congressman Al Gore to introduce the first witness.

Mr. GORE. We would like to call Dr. F. Gilbert McMahon from the Tulane University School of Medicine. Welcome, Doctor.

Without objection, the entire text of your statement will be put in the record and we invite you to proceed.

Mr. SCHEUER. Will the chairman yield momentarily?

Mr. GORE. Yes, sir.

Mr. SCHEUER. I am informed that in order for the electronic media to be present in the room, we need to get unanimous consent for that from the members. If there are no objections, so ordered.

Mr. GORE. Dr. McMahon, welcome. Those of us who follow this area closely are well aware that your name was prominantly mentioned as the new commissioner, and for reasons extraneous to the process of selection, you determined to take other options. You come with a distinguished record and, unlike some critics of the FDA, you have shown in your career a willingness to roll up your sleeves and get involved in trying to solve the problems that you have identified. That is most appreciated by those who are sincerely interested in improving the process. We are most pleased to have you lead off these hearings.

STATEMENT OF DR. F. GILBERT McMAHON, M.D., TULANE UNIVERSITY SCHOOL OF MEDICINE

Dr. MCMAHON. Thank you very much, Congressman Gore. I want to thank, also, Congressman Scheuer for having invited me to participate in your joint subcommittee hearings on "Pharmaceutical Innovation: Promise and Problems for the Eighties." It is an honor for me to be here. I sincerely hope I can make some contribution to your important deliberations.

I am certain we all seek the same objectives: better medications and more available for sick people. I say that as a physician, as an internist, a professor of medicine, and also as a patient who has to take heart pills every day. I speak as someone who has spent 32 years studying new and old drugs in man. I speak as one who has directed medical research programs within three major pharmaceutical companies, as one who has spent the past 15 years as a teacher at Tulane University, teaching medical students and physicians about the efficacy and the side effects of drugs. I speak as one who has often been a critic of FDA, but also as one who has testified in Federal courts as the FDA's expert witness.

On the subject of opportunities and breakthroughs for the eighties, I believe the decade of the eighties offers immense opportunities for many therapeutic breakthroughs. The fundamental methodology for new drug discovery has changed drastically in the past few years. Previously, pharmaceutical companies screened new chemicals randomly for biological activity in animals. Necessarily, there was a low yield of bioactive drugs and an even smaller percent of drugs that ultimately passed animal safety testing and went into human testing.

Today the approach for new drug discovery has changed from this chemical technology to a molecular biological approach. Specific functions of known chemical processes in the body may be augmented or blocked. Defective genes may be replaced in the future. With new biochemical, immunological, polypeptide methodologies, with new sophistication in recombinant DNA techniques, with new knowledge about specific receptor sites and enzyme activities, with recent discoveries about the slow calcium channel affecting the heart, we are now at the brink of major new drug advancements.

The potential exists for new antiviral and anticancer treatments and vaccines. We have new opportunities for producing natural polypeptides and hormones for treating and preventing inborn errors of metabolism, diseases of the aged, improving growth of dwafted people and improving treatment of heart disease. Indeed, there is now a backlog of important potentially "breakthrough" biologicals available in the pharmaceutical companies waiting to be tested in man.

New technology includes the possibility of producing large amounts of beef growth hormone and prolactin in order to increase meat and milk supplies for the world's hungry. New technology exists now for producing new antiviral and anticancer agents as gene products through DNA research. New neuropolypeptides produced by the same techniques offer new hopes in the treatment of neurological and mental diseases as well as new hopes for ultimate cures of such hereditary diseases as sickle cell disease, thalassemia, and even diabetes.

New drug delivery techniques—molecules designed to be carried and slowly released by circulating liposomes, microcrystals designed by physical chemists and encapsulated in tiny spheres which when applied to the skin will slowly and steadily release a medication over a period of weeks or months, so patients with chronic diseases won't have to swallow their pills every day but have them literally taped to their ear or their skin someplace once a week or once a month. There now exists an abundance of important new biological agents which need to be tested clinically in man, and therefore to benefit society and mankind.

The problems. I believe the IND–NDA process has become a bureaucratic monster. How does one convert new biological findings into medical utility? How can drugs expeditiously and safely be brought to the market? How can FDA cope with the truckloads of data they now require, particularly when they have current budgetary and personnel constraints, yet with their ever-present obligation to protect the public safety? Why is there now "Europeanization" of U.S. drug discoveries? Why is there now a drug lag? These are the problems.

Mr. SCHEUER. Would you elaborate on what you mean by "Europeanization"?

Dr. MCMAHON. I mean that over 50 percent of drugs that are discovered in Philadelphia, in Kalamazoo, in New York City, in American pharmaceutical laboratories, are studied first overseas. There is something wrong with a system, in my judgment, that causes that phenomenon. It's not a simple issue; it's not an economic issue; but it's a reality and we ought to think about why American technology is going overseas with American drug discoveries.

Essentially, one must prove a new drug to be effective and relatively safe. No drug will ever be completely safe. All drugs will always have side effects. The benefit, however, should exceed the risk. I have no quarrel with this at all.

But the system as now required by continuously escalating FDA regulations and guidelines has become inflexible, overburdensome, with too many nitpicking requirements.

The role of FDA in clinical research has become adversarial towards company discoverers of new drugs, towards institutional peer review committees who judge patient protection, and towards the 12,000 clinical investigators who administer new drugs to man. There is something wrong with a system that results in over half these drug discoveries having to be studied first in foreign countries. There is something wrong with a system that delays or denies many new important drugs being marketed here first, when they are discovered here first.

Why are there always 1,000 to 5,000 patients described in "New Drug Applications"? Side effects and efficacy can indeed be established with 500 patients carefully studied, and postmarketing surveillance is the only way to discern serious rare toxicity of drugs. Presently, all new drugs go through phase I, II, and III, beginning with tolerance in normal subjects and proceeding through controlled studies in gradually increasing numbers of patients and increasing numbers of investigators. But new flexibility ought to be available for the study of new gene products—for example, human growth hormones should be given to dwarfed people and not tested first in normal people; beef growth hormone and beef prolactin which may well increase the world's meat and milk supplies should not require studies of animal residual drugs, as after estrogens or DES.

The discovery in the past 4 years of genetically determined metabolic defects existing in 2 to 15 percent of the American population who fail to metabolize drugs like nortriptyline, sparteine, and desbrisoquine, and therefore this population develops more side effects, requires modification and flexibility in phase I and II studies of these classes of drugs. We are now entering a new molecular biological era where we don't need codes and guidelines as to how medical studies should be conducted. We need some flexibility and some commonsense.

In foreign countries, they often introduce the drug to a few patients with the disease to learn both tolerance, phase I, and efficacy, phase II, simultaneously. Many countries don't require submission and approval of all animal data and of proposed studies—a process that may take many months by the FDA—before the first

study in man can ever begin. They don't require 2 years of animal toxicity studies before beta-blocking drugs can be given patients for more than 30 days. They don't require physician-investigators to divulge patient names and confidential records unrelated to their research. They don't require Government inspectors to ask investigators "How busy are you?" They don't assume that busy doctors can't do clinical research properly, but rather, they believe that perhaps busy investigators just might be busy precisely because they are recognized as being good by companies who have a need to learn the truth about their new drugs—truth eventually obtains with all drugs—and indeed, companies have a monetary interest in learning what the drug does or doesn't do in man. Foreign countries usually don't require investigators to sign each page of 350 pages of reports on a 10-patient study. They don't require truckloads of raw data for new drug applications, particularly when an agency has neither the manpower nor the system to handle and assimilate such volumes of data.

We all agree, we want only safe and effective drugs on the market. We all agree that dishonest companies or dishonest investigators should be identified and disqualified. We all believe in protection of research subjects' safety and rights, the need for obtaining informed consent, and the need for review and approval of proposed studies by our peers prior to conducting studies.

Even the most severe critics of the present system of drug investigation acknowledge the track record for clinical drug research in the United States has, indeed, been remarkable. Not a single individual has died in the past 20 years as a result of phase I or II clinical drug studies. There are two equivocal exceptions to that, and I mention them in my statement. One fraudulently entered a research project at the NIH, and in the second instance, a clear relationship between the experimental drug and a young man's death was never clearly established.

On the other hand, people die every day because of the misuse or abuse of drugs. Some patients die because of the unavailability of new and better drugs.

By law, phase I and II studies are conducted necessarily by experts and are necessarily limited to small groups of patients. FDA should deregulate these early phases of clinical research in order to permit more drugs to be studied. Ninety percent of drugs studied in phase I and II fail ever to go into phase III or ever to become marketed products, primarily because of poor animal to human correlations of either safety or efficacy.

The problem of finding new breakthrough drugs and restoring American leadership in new drug discovery and therapeutic innovation can only be solved by permitting more drugs to be investigated in man. The present IND system must be changed, while not, however, sacrificing patient protection.

My recommendations: I would like to propose a deregulation of phase I and II, in order to greatly increase the numbers of drugs permitted to be studied here. This will increase the chances of discovery of new types of bioactive drugs, of drug breakthroughs, and of serendipitious discoveries. Phase I and II studies are necessarily conducted by experts, they are necessarily limited to small groups

of patients, and they have a great safety record. No one has died in 20 years in phase I and phase II research.

I would therefore urge the FDA minimize its involvement in phase I and II studies in the following manner:

Sponsors should submit only a brief notice of initiation of phase I–II studies. No actual protocols would be included with this material and no actual preclinical data. The responsibility for conducting the phase I and II studies safely rests with the clinical investigators, with the peer review committee, and with the company monitors, as the responsibility does, indeed, now. It doesn't rest with the Federal Government. It rests with the doctor doing the research.

Should any serious toxicity occur, of course, FDA would, as now, be notified immediately. Otherwise, only a summary of results of the entire data—preclinical and clinical—would be submitted with the phase III protocols, unless the drug is dropped from further study, in which case a notice of cessation would be submitted. This would replace the FDA workload imposed by handling some 1,000 new IND's a year currently for phase I and II studies, and would require perhaps handling only 100 per year.

Virtually everyone agrees that the present 8 to 9 years required for the total clinical evaluation of new drugs, including the 2½ year average time taken for NDA approvals, is grossly excessive and prohibitively expensive. It costs from $50 to $70 million per drug. And it denies useful new drugs to many sick people.

I wish to recommend the shortening of phase III clinical trials. The efficacy of a new drug is proven in phase II. The ultimate safety of a new drug is only proven in post-marketing surveillance. The purpose of phase III is simply to confirm efficacy and confirm side effects of a drug. This can usually be accomplished with only 5 to 10 studies, involving perhaps 500 patients, and 1 year's time. Phase III will be shortened if we accept the need for postmarketing surveillance, and if we limit the number of patients and studies needed in phase III.

New drug application consideration time needs to be reduced to within 180 days instead of the present average of some 24 to 30 months. Some new drugs like bethanidine, an antihypertensive available throughout the world for over 15 years, but not in the United States, and timolol, a new beta-blocker that reduces post-myocardial infarction deaths by 45 percent, are not yet approved by the Food and Drug Administration. These kind of delays are inexcusable.

I would like to propose several ways which might alleviate this difficulty: Require decisions within 180 days after submission; accept certified summaries of the new drug application, signed by a responsible company official. This would greatly relieve the FDA job of having to process 100 to 200 original NDA's a year, each consisting of truckloads of new data. FDA could always inspect companies and investigators, as now, to check actual raw data.

I would like to summarize, finally, in conclusion, my recommendations.

No. 1, deregulate phase I and II by reducing the IND requirements to simply a notice of initiation of studies.

No. 2, require, as now, a form 1639 to be submitted should serious toxicity appear.

No. 3, require only a notice of cessation on those 90 percent of drugs which fail to materialize in phase I and phase II; that is, the efficacy and safety simply are not there.

No. 4, require only a certified summary of preclinical and clinical data when a drug is proposed for phase III studies, with a phase III program outline to result in approximately 500 controlled patients for NDA submission.

No. 5, require only a certified summary for new drug applications.

No. 6, require NDA decisions within 180 days.

No. 7, require postmarketing surveillance for new drugs.

I have added an eighth one. The new FDA Commissioner, Arthur Hayes, is a man I respect and I know he has the confidence of the medical and scientific community. I hope you will give him the time and support to do his job.

Thank you very much for inviting me here.

[The prepared statement of Dr. McMahon follows:]

DRAFT

Gentlemen:

I want first to thank Congressmen Scheuer and Gore for having invited me to participate in your joint Subcommittee hearings on "Pharmaceutical Innovation: Promise and Problems for the '80s." It is an honor to be here. I sincerely hope I can make some contribution to your important deliberations.

I am certain we all seek the same objectives: better medications more available for sick people. I say that as a physician, an internist, a clinical professor of medicine, and I also speak as a patient. I speak as someone who has spent 32 years studying new and old drugs in man. I speak as one who has directed medical research programs within three major pharmaceutical companies, as one who for the past 15 years has taught Tulane University medical students and physicians about the efficacy and side effects of drugs. I speak as one who has often been a critic of FDA, but also as one who has testified several times as FDA's expert witness in Federal Courts (See Appendix #1: Curriculum Vitae).

Opportunities and Breakthroughs for the '80s

I believe that the decade of the '80s offers immense opportunities for many therapeutic breakthroughs. The fundamental methodology for new drug discovery has changed drastically in the past few years. Previously, pharmaceutical companies screened new chemicals randomly for biological

activity in animals. Necessarily, there was a low yield of bioactive drugs and an even smaller percent of drugs that ultimately passed animal safety testing and went into human testing. Today, the approach for new drug discovery has changed from this "chemical" technology to a molecular "biological" approach. Specific functions of known chemical processes in the body may be augmented or blocked. Defective genes may be replaced. With new biochemical, immunological, polypeptide methodologies, with new sophistication in recombinant DNA techniques, with new knowledge about specific receptor sites and enzyme activities, with recent discoveries about the slow calcium channel affecting the heart, we are at the brink of major new drug advancements. The potential now exists for new antiviral and anticancer treatments and vaccines. We have new opportunities for producing natural polypeptides and hormones for treating and preventing inborn errors of metabolism, diseases of the aged, improving growth of dwarfed people and improving treatment of heart disease. Indeed, there is now a backlog of important potentially "breakthrough" biologicals available in the pharmaceutical companies waiting to be tested in man. New technology includes the possibility of producing large amounts of beef growth hormone and prolactin in order to increase meat and milk supplies for the world's hungry. New technology exists for producing new antiviral and anticancer agents as gene products through DNA research. New neuropolypeptides produced by the same techniques offer new hopes in the treatment of neurological and mental disease as well as new hopes for ultimate cures of such hereditary diseases as sickle cell disease, thalassemia and even diabetes. New drug delivery techniques: molecules

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The Problems

The IND-NDA Process Has Become a Bureaucratic Monster.

1.) How does one convert new biological findings into medical utility?
2.) How can drugs expeditiously and safely be brought to the market?
3.) How can FDA cope with the truckloads of data they now require, particularly when they have current budgetary and personnel constraints, yet with their obligation to protect the public safety?
4.) Why is there Europeanization of U.S. drug discoveries?
5.) Why is there a drug-lag?

Essentially, one must prove a new drug to be effective and relatively safe (no drug will ever be completely safe), i.e., the benefit should exceed the risk. I have no quarrel with this. But the system as now required by continuously escalating FDA regulations and guidelines, has become inflexible, overburdensome with detailed nit-picking requirements.

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The role of FDA in clinical research has become adversarial towards company discoverers of new drugs, institutional peer review committees who judge patient protection, and the 12,000 clinical investigators who administer new drugs to man. There is something wrong with a system that results in half of U.S. drug discoveries being studied first in foreign countries. There is something wrong with a system that delays or denies many important new drugs being marketed here while often available several years earlier to patients in foreign countries.

Why are there always 1,000-5,000 patients in NDA's? Side effects and efficacy can indeed be established with 500 patients carefully studied, and post-marketing surveillance is the only way to discern serious rare toxicity. Presently, all new drugs go through phases I-II and III, beginning with tolerance in normal subjects and proceeding through controlled studies in gradually increasing numbers of patients with increasing numbers of investigators. But new flexibility ought to be available for the study of new gene products (e.g., human growth hormone should be given to dwarfed people and not first tested in normals; beef growth hormone and beef prolactin which may well increase the world's meat and milk supplies should not require studies of animal residual drugs as after estrogens). The discovery in the past 4 years of genetically determined metabolic defects in from 2-15% of patients who fail to metabolize drugs like nortriptyline, sparteine and desbrisoquine (and therefore develop high blood levels and more side effects) requires modification and flexibility in phase I-II studies of these classes of drugs. We are entering a new molecular biological era where we don't need codes

and guidelines as to how medical studies should be conducted. We need flexibility and common sense.

In foreign countries, they often introduce the drug to a few patients with the disease to learn tolerance (phase I) and efficacy (phase II) simultaneously. Many countries don't require submission and approval of all animal data and of proposed studies (a process that may take many months by FDA) before the first study in man can ever begin. They don't require 2 years of animal toxicity before beta-blocking drugs can be given patients for more than a single month. They don't require physician-investigators to divulge patient names and confidential records unrelated to the research. They don't require government inspectors to ask investigators "How busy are you?" They don't assume that busy doctors can't do clinical research properly, but rather they believe that perhaps busy investigators just might be busy precisely because they are recognized as being good by companies who have need to learn the truth about their new drugs (truth eventually obtains with all drugs) and, indeed, have a monetary interest in learning what the drug does, or doesn't do in man. They don't require investigators to sign each page of 350 pages of reports on a 10-patient study. They don't require truckloads of raw data for NDA's, particularly when an agency has neither the manpower nor the system to handle and assimilate such volumes of data.

We all agree that we want only safe and effective new drugs on the market. We all agree that dishonest companies or investigators should be identified and disqualified. We all believe in protection of research

subjects' safety and rights, the need for obtaining informed consent, and the need for review and approval of proposed studies by our peers prior to conducting studies. Even the most severe critics of the present system of drug investigation acknowledge the track record for clinical drug research in the U.S. has indeed been remarkable. Not a single individual has died in the past 20 years as a result of phase I-II clinical drug studies (one fraudulently entered a research project; and in a second instance, a clear relationship between experimental drug and his death was never clearly established). On the other hand, people die every day because of the misuse or abuse of drugs. Some patients die because of the unavailability of new and better drugs. By law, phase I-II studies are conducted necessarily by experts and are necessarily limited to small groups of patients. FDA must minimize its involvement in these early phases of clinical research in order to permit more drugs to be studied. Ninety percent of drugs studied in phase I-II fail to go into phase III or become marketed products, primarily because of poor animal to human correlation in either safety or efficacy. The problem of finding new breakthrough drugs and restoring leadership in new drug discovery and therapeutic innovation to the U.S. can only be solved by permitting more drugs to be investigated in man. The present IND system must be changed, while not, however, sacrificing patient protection.

Recommendations

I'd like to propose a deregulation of phase I and II in order to greatly increase the numbers of drugs permitted to be studied. This will increase the chances for the discovery of new types of bioactive drugs, of drug breakthroughs and of serendipitous discoveries. Phase I and II studies are necessarily conducted by experts, they are necessarily limited to small groups of patients. I would therefore urge that FDA minimize its involvement in phase I and II studies in the following manner. Sponsors would submit only a brief "Notice of Initiation of Phase I-II Studies". No actual protocol would be included with this material and no actual preclinical data. The responsibility for conducting the phase I-II studies, including patients' safety, informed consent, etc., would rest with the sponsors, the clinical investigators, and the institutional review committees. Should any serious toxicity occur, FDA would, as now, be notified immediately. Otherwise, a summary of the results of the entire data (preclinical and clinical) would be submitted with the phase III protocols, unless the drug is dropped from further study, in which case a "Notice of Cessation" would be submitted. This would replace the FDA workload imposed by handling some 1,000 new IND's/year for phase I-II studies, and require handling perhaps only 100/year.

Virtually everybody agrees that the present 8-9 years required for the total clinical evaluation of new drugs, including the 2½ years average time taken for NDA approvals, is grossly excessive, prohibitively expensive (i.e., $50-70 million) and it denies useful new drugs to many sick people.

We wish to recommend the shortening of phase III clinical trials. The efficacy of a drug is proven in phase II. The ultimate safety of a drug is proven in post-marketing surveillance. The purpose of phase III is to confirm efficacy and the principal side effects of the drug. This can usually be accomplished with only 5-10 studies involving approximately 500 patients and one year's time. Phase III will be shortened if we accept the need for post-marketing surveillance and if we limit the number of patients and studies needed in phase III.

NDA consideration time needs to be reduced to within 180 days instead of the present average time of 30 months. Some new drugs like bethanidine, an antihypertensive available throughout the world for the past 15 years, but not in the U.S., and timolol, a drug that reduces post-myocardial infarction deaths by 45% (N. Eng. J. Med. 4/2/81), but not yet approved by FDA. These kinds of delays are inexcusable. I'd like to propose several ways which might alleviate this difficulty:

(a) Require decisions within 180 days after submission.

(b) Accept certified summaries of the NDA, signed by a responsible company official. This would greatly relieve the FDA job of having to process 100-200 original NDA's/year, each consisting of truckloads of new data. FDA could always inspect companies and investigators (as now) to check actual raw data.

Summary of Recommendations

1. Minimize FDA involvement in phase I-II by reducing the IND phase I-II requirements to a "Notice of Initiation of Studies".

2. Require (as now) a Form 1639 to be submitted should toxicity or serious adverse reactions occur.
3. Require only a "Notice of Cessation" be submitted to FDA when a drug fails in phase I-II.
4. Require only a certified summary of preclinical and clinical data when a drug is proposed for phase III studies--with a phase III program outline to result in approximately 500 controlled patients for NDA submission.
5. Require only a Certified Summary for NDA's.
6. Require NDA decision within 180 days.
7. Require post-marketing surveillance for new drugs.

I believe sincerely that our present system has become overburdensome and over-regulated. It ultimately denies important new drugs to American patients. The role of FDA needs to be changed from that of adversary of industry, clinical investigators and peer review committees, to that of a catalyst for the expeditious delivery of safe and effective new drugs to the market. This needs to be done. This can be done.

Thank you for inviting me here today to participate in these important Hearings. I shall be happy to try to answer any questions.

F. Gilbert McMahon, M.D., F.A.C.P.
New Orleans, Louisiana

Mr. GORE. Thank you very much, Doctor.

You use the figure 2½ years for approval of new drugs. The General Accounting Office did a rather lengthy study of the subject for Chairman Scheuer's subcommittee and concluded that the average time for approval at the FDA was 17 months. Now, I guess there are figures all over the lot.

But can you tell us what the difference between their figure and yours might be?

Dr. MCMAHON. I use figures quoted by Dr. Wardell at Rochester, N.Y. Bethanidine was submitted as a new drug application 15 years ago. You see, when a company submits a new drug application, not infrequently the Food and Drug Administration asks for more data; therefore, the new drug application isn't officially submitted. This may go on, this ping-pong effect, for years and years and years.

In my experience, I think it's fair to say that it takes an exhorbitant amount of time. Once the FDA starts the clock officially with an NDA, certainly maybe the figure of 17 or 18 months for approval is valid. But many of them, too many of them, last years and years and years before approval. I think that's wrong.

Mr. GORE. OK. But you don't challenge the GAO's figures on that?

Dr. MCMAHON. Not at all.

Mr. GORE. They say 17 months of FDA time, and then 3 months of industry time. They have a number of specific recommendations, also.

Now, do you agree that there is no inherent conflict between insuring the safety and efficacy of new drugs and speeding up the time required for approval?

Dr. MCMAHON. I think no drug is ever completely safe. You can die of too much salt, of too much water. More people die from aspirin than they do of exotic new drugs. So I would say, with that background, realizing a drug is never completely safe and it might be misused, I would say that you can reduce the time and you can, while safely approving drugs, require a quid pro quo, postmarketing surveillance of new drugs. You can approve them, I think, with 500 patients instead of 1,000 to 5,000 patients.

Mr. GORE. Well, there are two different approaches possible. I believe that we can insist that the process become more efficient and that undue delays be eliminated, without compromising safety and efficacy.

On the other hand, there is the approach that would take an increased risk with the public safety on the argument that a quicker approval, the benefits of a quicker approval, would outweigh the extra risk and that postmarketing surveillance would pick up those injured by the rapidly approved drug and the damage would be minimized.

Now, are you choosing the latter approach?

Dr. MCMAHON. No. I think the public ought to share an increased risk with every new drug, whether there are 500 patients studied or 5,000 patients studied. It would take the study of 1.5 million patients to detect the toxicity of chloramphenicol chloromycetin, for example, which has an incidence of 1 in 30,000, 1 in 50,000,

of blood dyscrasias and serious blood diseases. So you only learn that after marketing.

I would hope that the public and doctors generally could share some extra risk for the possible benefits of a new drug being available years before. It bothers me that calcium antagonists are on the markets around the world, calcium-blocking agents, and not in the United States. People leave this country to get drugs for heart disease because they're not available in the United States. There's something wrong there.

I think, on the other hand, the public is a little naive—and a lot of doctors are, too; they think drugs are always safe when they're put on the market. Safety is relative, and the benefits, I hope and believe, by the present system, even, should exceed the risk and generally do. But when you put it on the market, then it goes into hundreds of thousands or even millions of people and patients and I think we learn the real rare serious toxicity and occasionally you have to withdraw a drug from the market.

You can't just give more work to the FDA. They have constraints. You can't require the present workload of the FDA. They have too many constraints. I think we have to ease the workload on the FDA by reducing the requirements and letting the public and patients share some of the extra risk for a year or two after a new drug is on the market.

Mr. GORE. Well, I guess I want to explore further—not completely today—but I would like to explore further exactly what is being proposed by the public sharing more of the risk.

To the extent that the public shares the risk, do you agree that the public should be given more information about the risks associated with drugs that are sold to them?

Dr. MCMAHON. I believe that a patient has a right to know about his drugs, yes, sir. I do not believe that the patient package insert is the best way to inform patients, by compulsory mandate of the system that hasn't been tried. I think patient's information about a drug is an important thing for some patients, and for some patients they don't want to know and they could get worse with that knowledge of a possible litany of side effects, especially when you don't have numerator and denominator data. Some people die from water and from aspirin and from penicillin. Are you going to tell them that?

Some people can take it. Some people would share the responsibility of having a 1 in 10,000 chance of an anaphylactic reaction from penicillin and maybe dying. But some people, you wouldn't want to tell them that. It would make them 20 times worse than their pneumonia or sore throat maybe. So I would leave that to the doctor at the bedside, not to a dictate from the Federal Government. I think the practice of medicine is a patient-to-doctor problem and it ought to be handled at the bedside and not by dictum from the Government.

Mr. GORE. Of course, I don't want to open up the debate on patients package inserts at this hearing. There will be plenty of time to explore that issue.

Of course, I can't resist saying that what was proposed was to try out that method and see how it worked, and now the industry has succeeded in preventing even the trial from going forward.

Dr. McMAHON. The original proposal was to do it.

Mr. GORE. Yes, but the amended proposal, which has not been halted, was to try it with 10 and see how it works, and the industry succeeded in preventing that from happening so far.

Now, the essence of your testimony is that because of the revolution of knowledge in this field, and particularly the dramatic new developments in our understanding of DNA and of biology and chemistry generally, the pharmaceutical industry is on the verge of introducing a whole new wave of what used to be referred to as "wonder drugs" that will provide almost miraculous cures for a number of ailments that are now intractable; that in anticipation of these new advances, the Congress ought to devote some attention to the lengthy delays that now occur in the FDA approval process, and you are offering specific recommendations on how to remove some of those roadblocks?

Dr. McMAHON. Yes, sir.

While I still believe—and I'm sure you would agree—that it's essential that patient safety be protected, I am suggesting that when I give a new blood pressure lowering drug to a patient, it is really my responsibility there, with the company monitor, the discoverers, and the doctors who got it from the company, it is our responsibility there to do it safely. It isn't the Government's responsibility.

I would suggest that we have had 20 years of very safe human research in this country because of doctors taking good care of patients, because of peer review committees and so on, not really because of Federal legislation. In fact, I think it's running it out of the country and we're losing technological leads where there is a drug lag.

Mr. GORE. One final question.

How extensively is postmarketing surveillance now being carried out in the United States? There's very little of it, isn't there?

Dr. McMAHON. Well, I was a member of Senator Kennedy's Joint Commission on Prescription Drug Use, and I went along with the recommendations our Commission made. It would require the establishment of a nongovernmental, private agency, or quasi-public agency, and so on, some obstacles which aren't imminently to be acted upon. I think a lot of progress has been made by the Food and Drug Administration in taking some leadership in postmarketing surveillance. I think the job the FDA did with tricrymaften (selacyrn), new blood pressure lowering drug from Smith, Kline & French, and removing it from the market when hepatitis was identified, they are to be congratulated and I told them so.

I think there is postmarketing surveillance going on in the United States. By postmarketing surveillance, there are numerous avenues of approach, numerous ways in which it must be done. I think the system the pharmaceutical industry uses and doctors use through medical journals generally works. It needs to be improved, of course. But I don't think it's a major problem.

What I would like to see done or see required is as a quid pro quo for getting drugs on the market sooner, to require postmarketing surveillance be done on virtually every new drug.

Mr. GORE. Thank you very much, Mr. Chairman.

Mr. SCHEUER. Thank you, Mr. Gore.

On this question of postmarketing surveillance, if we were to rely on postmarketing surveillance rather than endless months of premarketing paper shuffling between the FDA and the companies, do you think we would have to describe the kind of environment in which some of these dangerous drugs are used? Should they be prescribed, for example, only by the doctors who have special training and experience in using some of these esoteric new drugs? Or should they be prescribed in a hospital setting, where the patient comes to the hospital regularly, subject to the scrutiny of perhaps several highly trained doctors in the use of these drugs?

Or would you say the one-half million doctors in this country licensed to practice medicine, are they qualified both to prescribe drugs and to be a part of the postmarketing surveillance system by scrutinizing the patient for side effects? Are they qualified by training and experience to do that?

In other words, what I'm groping for in this awkward way, if we're going to rely heavily on postmarketing surveillance, do we have to limit or further define the postmarketing surveillance system?

Dr. McMAHON. That's a difficult question, Congressman, and I can't pretend to answer it glibly or sufficiently in a few minutes, or extemporaneously.

I think, in general, I like to see doctors have the right to give drugs wherever they practice. I hate to deny a patient in Bogalusa, La., an anticancer drug just because there isn't an oncologist cancer specialist in town. In general, I wouldn't want to deny the patients in rural America the availability of new drugs because there isn't an expert in town.

On the other hand, I can conceive of circumstances where with the introduction of a new anticancer drug or some unusual drug used in emergency situations being initially restricted to certain doctors and certain hospitals to learn about the postmarketing surveillance under rigid conditions. So I think you have to be flexible. That's what I would like, not a lot of guidelines from FDA, not a lot more codes and minutia, which are inflexible. Put some flexibility and some commonsense in. I'm sure it could be worked out on an individual basis.

Mr. SCHEUER. The question is, How do we work out a system that provides for that flexibility on an individual basis? It surely doesn't exist now.

Dr. McMAHON. No, sir.

Mr. SCHEUER. Is the problem that under the legislative mandate the FDA cannot legally inject into their system the flexibility and the honest commonsense judgment that you're talking about, or is it a disposition not to use judgment and flexibility that is perfectly available to them?

Dr. McMAHON. I'm a little sympathetic for that bureau director down on the bench at FDA who has to decide that this new drug should be on the market or not and make a recommendation to his bosses. That's an awesome kind of responsibility. I'm sympathetic toward him.

I think we would share the burden of his permission to get it on the market if we didn't put him at risk alone. That is, if we required that new drugs on the market have to be recognized as new

drugs—maybe in the advertising, maybe in the kind of labeling it gets, and let doctors and patients know that there's a little extra risk for the first 2 years, any new drugs on the market——

Mr. SCHEUER. In other words, rely on the postmarketing surveillance?

Dr. MCMAHON. Yes, sir. I think it can work.

Mr. SCHEUER. How about some shared decisionmaking? How about using some of the talent out there?

Dr. MCMAHON. There's an awful lot of talent in America.

Mr. SCHEUER. In the case of an individual patient or a small group of patients, isn't it conceivable that—not only, say, an individual patient, but let's say a child who suffers from a disease, epilepsy, for example, to which he has an allergic reaction to the antiepileptic drugs that are available in the States now—there may be antiepileptic drugs being used abroad designed for young children who are allergic to epileptic drugs that are in use here?

Now, it's true that that drug that has been in use abroad takes 10 to 15 years getting approved here because the FDA doesn't choose to give validity to the experience abroad, and doesn't choose to give validity to the epidemiological studies underlining that drug's approval, even though they have clear jurisdiction under their statute to recognize foreign medical studies. Do you think in a case where, let's say, an antiepileptic drug has been used overseas successfully for many, many years in developed countries, and when a young child is allergic to all of the other drugs that have been approved, that perhaps some of that talent out there might be harnessed to make a decision as to whether this child's life-health prospects would be enhanced or reduced by the availability of that drug, whether for his consolation of risks and benefits, that foreign drug is clearly indicated?

Might it be possible to create by regions some kind of a peer group committee, composed of a dean of a school of pharmacology, perhaps the head of a county medical society, perhaps the head pharmacologist, neuropsychopharmacologist in the drug company that's purveying the drug, and perhaps introduce an ethnicist also, and perhaps let that ethnicist and medical school dean and the dean of the county medical society and the top pharmacologist of the company that's purveying the drug and the patient's own doctor, to allow that consortium of talent to make the decision as to whether under all the conditions prevailing, with that child's medical history, whether the risks and the benefits of using that foreign drug with its history of safe usage over many, many years would justify a decision to use it, and whether we might not create a system where that commission or that committee or that peer group would recommend to the FDA that that child or that small group of patients similarly situated should use that drug, perhaps subject to scrutiny in a hospital environment and with prompt reporting to FDA of any negative fallout?

Dr. MCMAHON. I have found many times in my life where I had a need for an emergency issuance of a drug, or the availability of a drug, under emergency circumstances, both in my family and in my patients. When I pick up the phone and call somebody at the FDA, I have been able to get the drug under emergency circumstances.

In my experience, the FDA has been very cooperative with us on a unique need for a drug. So I haven't found that a terrible impass.

I think FDA needs help, though, on your other point, and needs advice and needs reassurance. They go by the book. They go by the letter of the law. The letter of the law says you have to have controlled studies, double blind generally, and proof of efficacy and safety before they can approve a new drug. I think it's a little too literal and I think some individuals operate a little bit more severely than that within FDA. That is, they want to know what contribution a fourth or fifth beta blocker or thiazide diuretic will make to the American patients. I don't think FDA individuals have that authority to judge relative efficacy and safety. That isn't the mandate; that isn't the letter of the law. But that's how some of them function.

I am optimistic that Dr. Hayes will change that interpretation of the law by some of his people, which delays getting new drugs out there and getting more of the same. You only learn whether a drug has unique properties after it's been marketed. You only learn unexpected and novel new drug uses and new benefits of old drugs after—sometimes it's been 10 years on the market.

Mr. SCHEUER. Dr. McMahon, we're running short of time and we have other witnesses and other members who want to question you, so I'm going to ask just one more question. But I am going to ask unanimous consent that if any of the members wish to, they may submit questions to you in writing. That will apply to the other witnesses as well, and we'll hold the record open for 10 days or 2 weeks, so that any members who wish can get their questions to you and can get the answers printed in the record.

I'm just going to ask one more question at this time, and that is, you have told us that in the last decade or so there hasn't been a single death——

Dr. MCMAHON. That's right.

Mr. SCHEUER [continuing]. Incurred due to the research, development and production of these new drugs. Yet you have described the enormous time gap of 10 to 15 years and the enormous investment required of $50 to $70 million in the development of new drugs in this country.

Now, abroad, in the advanced developed countries, where drugs are approved in a far more rapid process—and this includes Europe, Scandinavia, Japan, Australia, New Zealand, and Canada—have you found that the flexibility of their system and apparently the ability of small advisory groups to make important recommendations that are followed generally in those countries, have you found that that has produced a different history than we have in this country?

In other words, have they suffered serious injury and death as a cost of the enhanced speed with which they have approved these drugs? What has the risk-benefit calculus been for those countries that have opted for far more swift processes of new drug approval?

Dr. MCMAHON. It is my thesis that more good has been done than harm. There are, of course, horror stories like practalol, which was marketed in the United Kingdom and never marketed in the United States, a beta blocker for hypertension and arrhythmias and angina pectoris for heart patients. But the side effects

were picked up and it was taken off the market. That's the bad side.

The good side of the news is they had beta blockers on the market for people with heart disease 10 years before we did, lives that are lost by the unavailability of those drugs is indeterminant, but real.

Mr. SCHEUER. Were lives lost in the initial instance when the drug was placed on the market before its recall?

Dr. MCMAHON. Yes. A few people lost their sight, and some of them had peritoneal fibrosis, and I'm sure a few lives were lost with practalol. But many, many lives were saved using it as an antiarrhythmic, using other beta blockers——

Mr. SCHEUER. So you feel, as a matter of judgment, that the very much more efficacious and swift approval process overseas, on balance, has been life enhancing and health enhancing?

Dr. MCMAHON. Yes, sir.

Mr. SCHEUER. Thank you very much, Doctor. Your testimony has been most stimulating, indeed.

Congressman Carney.

Mr. CARNEY. Thank you, Mr. Chairman.

If I may, Doctor, I would like to get a little personal. You said in your statement that you are a cardiac patient, is that correct, and you take daily medication?

Dr. MCMAHON. I tell doctors when I talk to them that if you live long enough you begin to deteriorate, and if you're real lucky, you begin to have to take pills. When you consider the alternatives, it's better to take pills than the alternatives. [Laughter.]

Yes, sir, I have had to take heart pills for several years. It's quite a life.

Mr. CARNEY. The problem that you have with your disease would be one that could be helped by taking the calcium-blocker medications that are available in Europe?

Dr. MCMAHON. It may well be.

Mr. CARNEY. Or the beta blockers?

Dr. MCMAHON. I take a beta blocker, and I take quinidine, an old drug, and I get by. I don't like to talk about my personal health in front of a TV camera, but I think there are better drugs in Europe for my problems, yes, sir.

Mr. CARNEY. That's the question. I didn't really mean to get personal. I can understand it.

Maybe this will help. I have the same problem that you have——

Dr. MCMAHON. You look healthier. [Laughter.]

Mr. CARNEY. Well, I've probably had it longer than you have and I have learned to live with it. But I've had a couple of coronaries myself several years ago. I was just curious about you, as a physician. Would you take those drugs that are available in Europe now that are not approved in the United States to alleviate angina or something like that? Do you feel personally that they have done enough research on those drugs for them to be safe for consumption here and would you be one to take it?

Dr. MCMAHON. Indeed. That's an interesting story, and since you asked me, I'll tell you what I did. About a month ago I called a friend in the pharmaceutical industry and asked him to send me a calcium slow channel antagonist, a drug which hasn't been ap-

proved in the United States but which is on the market in many countries in Europe. This was an emergency IND thing and I wasn't doing real well with the current medications available in America, and with a competent cardiologist treating me.

Well, he mailed me the drugs very promptly, and he mailed me so much paperwork, with so much redtape, that I have refused—and I didn't intend to bring this subject up, but I'm going to give it to you—there was so much redtape for me to take that new drug, I don't want to bother. I just refused to bother with that. It's too much redtape.

Mr. CARNEY. There's redtape on this end here——

Dr. MCMAHON. The Food and Drug Administration requirements for me to take that medicine, it isn't worth it. I'm sorry. It ought to be available in my opinion, and it's a shame it isn't available.

Mr. SCHEUER. Will the gentleman yield?

Mr. CARNEY. Yes, I will yield.

Mr. SCHEUER. Doctor, I wonder if you would be willing to give us the file that you had to fill out, which you didn't fill out, to be part of the record?

Dr. MCMAHON. Yes, sir, I can mail it to you.

Mr. SCHEUER. I wish you would, and we'll make it a part of this record. This is exactly what we're getting after.

Dr. MCMAHON. It's wrong. Commonsense isn't there any more, that's all. But I am sympathetic with the FDA doctor who, you know, goes by the book. It's the law that needs changing, and it isn't all their fault—I think that's glib. It isn't all the fault of the FDA. The system needs to be changed, and I think it will save lives and it will reintroduce some American leadership in medical discovery if we can change the regulations and change the way they operate.

Mr. SCHEUER. I want to say that I resent the fact that my colleague, Congressman Carney, asked so much better questions than I did, that he elicited these marvelous answers from you.

Mr. CARNEY. Well, Mr. Scheuer, I paid a big price to have the knowledge to ask that question. [Laughter.]

I had two heart attacks and open heart surgery, so I have a feeling for the good doctor down here and I understand what he's going through.

What you have described to me I would not think would be categorized as a compassionate drug or an orphan drug here in the United States, but a drug that just has not gone through the necessary redtape to be approved for consumption by American patients; is that true?

Dr. MCMAHON. Mind you, I am not in a position of seeing all data available to the Food and Drug Administration. I think it's superficial of me to always criticize what their data is on this blocking agent verapamil and other blocking agents, naphididine and so on. You know, I don't have all the information. FDA does.

But I believe it has been available long enough and it is in enough markets around the world. I certainly would like to try it, but I don't want to have a lot of cumbersome work.

Mr. CARNEY. Another question I would like to ask, a hypothetical question, and it would be one that I think everyone could appreci-

ate because I would suspect everyone has used this drug, and that would be aspirin.

If aspirin were unknown to the medical community today, and someone found or discovered aspirin in a clinical atmosphere in one of our leading universities, attached to a research medical facility, could you project how long it might be before aspirin would be put on the market or if, indeed, it would ever get on the market?

Dr. McMAHON. I think it's a classical question, and I'll give you the classical answer. It may surprise you.

Yes, I think it would get on the market, but it would be for which claim? If you want to prove it lowers fever, you would get it on the market in 7 to 10 years and spend $50 million. If you want to prove it relieves pain in arthritic patients, that would be double those costs. If you want to get the claim that it is anti-inflammatory, you do the studies all over in inflammatory disease like rheumatoid arthritis. If you want to prove it's antiplatelet adhesiveness properties diminish coronary artery disease, you might be spending billions of dollars, I think, and virtually no one can afford to do those kinds of studies, that indeed people are benefited by taking two to four aspirin tablets a day after having had a single heart attack, which many doctors in this country believe. I think the FDA now believes the data and has made this concession to the aspirin manufacturers.

So I think it would be a very difficult thing, but I think it really would get on the market, yes, sir, sooner or later.

Mr. CARNEY. That's amazing, though, when you consider the cost and time involved in that, to get that drug on the market.

I guess, as a drug that would relieve temperature, it could be a life-saving drug. We don't think of it as being a life-saving drug in everyday use, but it certainly could be a life-saving drug and we would be keeping that drug off the market for, as you say, 7 years and $50 million for the proof that it does reduce temperatures in the body and forget the other benefits of the drug because that would be——

Mr. WALKER. Would my colleague from New York yield for a moment, please?

Mr. CARNEY. I would be glad to yield to my colleague from Pennsylvania.

Mr. WALKER. Just one followup question, if I could, on that.

How much would aspirin likely cost the consumer after going through that whole process that you described?

Dr. McMAHON. Fifty cents a pill, as a guess. It would be outrageous.

Mr. CARNEY. And they're 89 cents for 250.

Dr. McMAHON. The patient ultimately pays. With the continued studies necessary, you're only hurting patients in the long run. You're hurting sick people.

Mr. WALKER. I thank the gentleman for yielding.

Mr. CARNEY. Doctor, I could ask questions all day, and I know my colleagues have some. I will ask one final question, although it generally gets away from the specific problem that I was trying to get to.

This concerns the transfer of pharmaceutical technology to medical practitioners. How much of a problem do we have there, even in close proximity to medical centers, and then how much of a problem do we have when we talk about rural America and the application of medicine in rural America?

Dr. McMAHON. You mean when a new drug is introduced?

Mr. CARNEY. Proven and the whole thing. I mean, this drug is now accepted——

Dr. McMAHON. You mean the scientific process, where once a drug is on the market, how long does it——

Mr. CARNEY. Right.

Dr. McMAHON. Well, doctors have to read about it in the journals, and doctors have to learn about it from other people. I think drug detail men perform a service, and I tell my students that shouldn't be your only source of information. We all have biases, and I am sure a drug detail man has some biases, and you ought to read the journals and read the package insert and learn about the drug from multiple sources.

But in general, I think with the present mechanisms, doctors are aware of new drugs pretty rapidly and I don't think there's a big vacuum there.

Mr. CARNEY. By what process do they gain their knowledge of the new drugs?

Dr. McMAHON. The medical journals and scientific literature. They learn of new drugs by drug detailing, and attending seminars and by continuing medical education programs they learn of new drugs.

Mr. CARNEY. In rural medicine, they are so overwhelmed with the lack of qualified medical practitioners in rural America that they're working 15, 16 hours a day.

I had a doctor once tell me that before—and this was a doctor who practiced in rural America in pediatrics—he told me—and this was the truth, a physician I served with in the service—he said, "Bill, oftimes it's necessary for me to be the first one in my community, because it's so large a community and the hours I have to serve, I have to make sure I'm the first one in my community to read 'Readers Digest.' "

Dr. McMAHON. That's true.

Mr. CARNEY. Is there much truth to that statement today?

Dr. McMAHON. Yes, sir.

Mr. CARNEY. This was a long time ago.

Dr. McMAHON. Patients frequently are interested in learning about drugs, and everybody's family has some illness sooner or later, and people are interested in drugs and the treatment of their diseases.

Mr. CARNEY. Doctor, your testimony has been just outstanding. As the chairman suggested, I'm sure I will be writing many questions. But I would like to yield to the rest of my colleagues.

Mr. SCHEUER. Congresswoman Claudine Schneider of Rhode Island, a very distinguished and active and contributing member of this subcommittee.

Mrs. SCHNEIDER. Thank you, Mr. Chairman.

I have some very speedy questions I would like to ask you.

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Getting back to the redtape, I just want to clarify in my own mind if you feel that the obstacle to drug approval lies in statutory flaws or do you feel it's in the regulatory realm of bureaucratic organization?

Dr. McMAHON. I think it's in both places. I think changing regulations will be required, particularly with my recommendation for the IND process. That is the regulation that has to be modified or eliminated.

The other thing is, I am confident that the hesitancy of some FDA reviewers in approving a drug for marketing would be minimized if we could share with them the responsibilities somehow of occasionally making a mistake, like with Ticrynafen or Selacryn, a drug out on the market and within a year there were a few cases of hepatitis and it was removed from the market. But I think we, as patients and doctors and the public generally, ought to be willing to share the benefits of a new drug and having it available for people in whom generally there would be a great deal of benefit for the extra occasional risk.

Mr. SCHEUER. You characterized that act of approving a new drug, where some adverse actions did appear, as a "mistake"——

Dr. McMAHON. No, sir.

Mr. SCHEUER. No, you said——

Dr. McMAHON. Well, I didn't mean it.

Mr. SCHEUER. I didn't think you meant it. Because what you're talking about is a system that provides for some trial and error on the assumption that overall the benefits are going to be far greater than the occasional setback.

Dr. McMAHON. That's right. What I meant is we lack clairvoyancy. We don't know until patients, maybe 100,000 or 1 million people, have been given the drug. You're right. Until then do we not know and we won't know the rare serious toxicity of new medicines.

But I think the overall good would be tremendous, and the FDA reviewers would be encouraged to know there's a system of postmarketing surveillance intact and that, you know, it isn't all his fault if——

Mrs. SCHNEIDER. Where does the system exist for postmarketing surveillance? Give me a country that has a good network of information.

Dr. McMAHON. Sweden has a good postmarketing surveillance system. The British Empire has—the United Kingdom has a good postmarketing surveillance system.

Mrs. SCHNEIDER. Could you just rapidly outline what that system might involve?

Dr. McMAHON. There's a yellow card system that the medical director of the system in the United Kingdom described to our Joint Commission a couple of years ago. There are a number of doctors who routinely send in yellow cards when they notice reactions to drugs in England. They review them. They have a small office with maybe one-half dozen people, not millions of dollars, not a big, bureaucratic empire, but a small little office of people. They send out pharmacists and employees in their office to check these little yellow flags that go up when somebody has an unexpected effect

that may be related to the drug. They get the raw data and they do their best to learn whether it's cause and effect.

I think that's a good system. It's entirely socialized in Sweden and they know, therefore, the denominator and the numerator, that maybe 48,000 people are taking the drug every day and, you know, if one person gets a reaction, they have some real statistics.

We have trouble in this country in getting data, numerator and denominator data, on side effects of drugs. I think gradually we'll get it, but it's a complex issue.

Mrs. SCHNEIDER. But if we had a surveillance system, we would have to have that in place also, would we not?

Dr. MCMAHON. Well, I think it's evolving. I think we're doing a much better job—companies and FDA, for example, and doctors generally—today than we did 5 years ago.

Mrs. SCHNEIDER. OK.

One short question. Insofar as concerns decisions on new drug applications, I thought that the Food, Drug and Cosmetic Act required decisions to be made on new drugs within a period of 180 days.

Dr. MCMAHON. You're right.

Mrs. SCHNEIDER. Doesn't that happen?

Dr. MCMAHON. Not in practice. It depends on when you want to set the clock. If you keep setting those 180 days back because you ask more questions of the company, and they submit more information——

Mrs. SCHNEIDER. Oh, so they set it back after additional inquiries.

Dr. MCMAHON. It's meaningless. Drugs aren't approved in 180 days.

Mrs. SCHNEIDER. I see. OK. Thank you very much. I appreciate your information.

Dr. MCMAHON. Thank you, Mrs. Schneider.

Mr. SCHEUER. Congressman Bob Walker of Pennsylvania.

Mr. WALKER. Thank you, Mr. Chairman.

I would just like to know about the kind of drug that you might not be able to show as clinically effective, but yet might have some application. I'm thinking of a drug like laetrile. Where does that fit into the whole process, where a patient may feel as though they get a significantly enhanced effect from the drug, mainly because they believe in it, and yet it is difficult to show there is any clinical effectiveness to it whatsoever.

Where does that fit into this process?

Dr. MCMAHON. It's a very profound question. The National Council of Drugs, to which I belong, wrestled with it. Our recommendation was, as the FDA's recommendation, was that laetrile should not be available to patients in this country.

There is no proof that laetrile does any good. There is no evidence in the world literature that it does good. I'm not sure where it goes. I think the question really is, to what extent should the Federal Government protect people against themselves. I have no glib answer to that. Maybe a patient should have a right to hurt themselves, I don't know. I hope not.

Mr. WALKER. What if you have a terminal patient in the eyes of the medical community and he requests such drugs; what do you

think the role of the Government is in that area, particularly if there's proof that it doesn't do any harm, either?

Dr. McMAHON. Well, there isn't in the case of laetrile. But in response to your question, I hope the role of the Government in patient care is minimal. I create addiction in some people with widespread cancer, and I'm delighted to ease their pain. What's a doctor for? I hope the Federal Government never has to tell me, you know, what I'm going to do with a particular patient with drugs that are on the market. I think the Food and Drug Administration must resist the temptation to get into patient education and patient care.

Their assignment, to me, is to judge the safety of devices and drugs and foods, and whether they're safe and effective. But to get to the level of the bedside, I hope they resist that temptation. That ought to be left up to our doctors and all the circumstances that vary with each patient and each doctor.

Mr. WALKER. We recently heard testimony that an NDA drug was known to cause renal failure, but investigators weren't warned about that particular aspect of it. How can something like that happen?

Dr. McMAHON. I don't know. I think that's a tragedy and I sure would look under that rock and try to find out.

Mr. WALKER. Well, where's the protection for the public in that context?

Dr. McMAHON. The companies I am familiar with on a periodic basis have the requirement and comply with the requirement to report serious, new adverse drug reactions to the Food and Drug Administration. When a new drug gets on the market, the requirement is that every 3 months for the first year or two, and then every 6 months every year afterwards, you send in toxicity reports. I find it quite inconceivable that any major American pharmaceutical manufacturer would not send in data. It can happen, it's conceivable. Maybe that isn't the right word. But it is certainly a rare thing in my judgment, in my experience.

Mr. WALKER. Thank you, Mr. Chairman.

Mr. GORE. If the chairman would indulge me, I would like to pursue this instance because——

Mr. WALKER. I would be glad to yield to the gentleman.

Mr. GORE. Thank you.

My colleague and I were involved in a hearing where this example that he mentioned came up. It was methyl CCNU, if my memory serves me correctly, an experimental anticancer drug. What happened was that the drug was approved for experimentation, experimental use, and a number of infants around the country experienced kidney failure. The mother of one of those infants was concerned that she had not been told about any risk of kidney failure. She pursued it with the National Cancer Institute and the FDA.

They were able to establish that there was a risk only by going back to the basic research involving the rat studies; they found that in 5 out of 5 rat tests kidney failure was present, a 100-percent rate. It was just lopped off.

Now, if your recommendation to have only a notice of initiation of those early stages on file was taken, then that mother wouldn't be able to find those rat studies, would she?

Dr. McMAHON. Well, No. 1, I assume the child was dying of metastatic cancer——

Mr. GORE. Let's make that assumption. I do not know that to be the case.

Dr. McMAHON. And I don't know all the circumstances. But the CCNSC, the cancer chemotherapy group, kind of operates, in my experience—and I'm not an expert on how they study cancer drugs—but I believe it is pretty much outside the realm of the usual drug investigation going on with all noncancer drugs. I have never studied an anticancer agent in man experimentally, and I don't treat cancer patients generally. But I think they have a system, a regional system, their own IND's and NDA's. I don't think they go through the FDA ordinarily. I think the—somebody who knows the National Cancer Institute should comment on that. But I don't think they have the same constraints that we do with new drugs generally.

Mr. GORE. Well, the point that I think is made by this, is that there are incentives by researchers and incentives for companies to use the public as the laboratory to test products that have some risk associated with them.

Now, if you're talking about significantly increasing the risk which is passed on to the public, then I think that we need to proceed somewhat cautiously.

Now, isn't it true as a matter of course that patients taking experimental drugs are required to sign a legal liability release form absolving companies?

Dr. McMAHON. No, not at all. But there are other constraints that I gather you're not terribly familiar with. The informed consent, the peer review of an institutional objective committee with societal representatives and lawyers and ministers as well as physicians——

Mr. GORE. I understand that's a requirement. What about liability release? Are such forms commonly used?

Dr. McMAHON. No, sir. In fact, it's excluded by FDA regulations. You can't make a statement of liability release.

Mr. GORE. Does informed consent serve that purpose at all?

Dr. McMAHON. Informed consent is to tell the patient in his or her own language the possible risks of the research. When you get into the field of cancer, you have another ball game. I am not deeply familiar with it. But these are people who are often dying, who have widespread disease, who get these drugs, and whether the drug caused the problem or whether the disease caused the problem is often very difficult to ascertain.

Most people who are studied by the American Cancer—by the CCNSC program—get multiple drugs, not one drug. We would not—no peer review committee in the United States would approve studying a drug that had kidney toxicity in animals, to give it in man. The cancer role, I don't know about, but the other real world, where 99 percent of the drugs are studied in noncancerous patients, it would never——

Mr. GORE. I think it was a mistake.

Dr. MCMAHON. Yes, sir, I think so, too. No drug is given to people without informed consent of the individual, the review of a peer committee of people removed from the research, and I think it is done safely. It has not resulted in death and——

Mr. GORE. Let me clarify the last point, though.

Is it not a fact that the informed consent does serve to limit the liability of the company if the patient signs the informed consent form and says "I acknowledge the risks, I accept them" and so forth?

Dr. MCMAHON. That isn't why we use it.

Mr. GORE. Well, I'm not saying that——

Dr. MCMAHON. I'm not a lawyer and I can't answer whether it reduces liability. I'm a doctor and I can tell you the purpose we use it and med schools use it is to inform the patient of their rights and what the possible advantages or disadvantages of that drug are and what the risks are of that drug, so they can intelligently participate or walk away from that study.

Mr. GORE. I just want to make a point, briefly, that most patients, if advised by their doctors that this particular medication is experimental in nature and "we think it might help you, and you have to sign this form, I am going to explain to you the risks which may be associated with this in my considered judgment. You ought to make the decision, but I would advise you to do it," most patients are going to do it and they're going to sign the form, and they do so currently with the knowledge that the FDA is pretty rigorous in requiring safety of new drugs, and if we're going to change that standard, then we should do so I think with a great deal of caution and not simply under the banner of deregulation.

Dr. MCMAHON. Yes. I am sympathetic but not entirely in agreement. I think doctors sometimes intimidate patients, of course, and I think you're suggesting it's a more frequent occurrence than I am.

Mr. GORE. I wouldn't use the word "intimidation." I think it's more——

Dr. MCMAHON. Well, please sign the form. You know, when you have a doctor-patient relationship, I think it's intimidation, the scene in the scenario you describe.

We have a nurse sit down with the patient and explain the form. They feel—I think the best evidence there is no intimidation is that many of our patients aren't interested in participating in drug studies where the drug may lower blood pressure, and good for them. You know, I think they should have the right to walk away. In fact, it's required by law and by practice and by peer review committees, that the patient in the informed consent understands he may or may not participate, and he can leave the study at any time he wants to.

Mr. GORE. Thank you very much.

Mr. WALKER. Mr. Chairman, if I might just follow up, to go back to the renal failure, we acknowledge there may be a mistake involved in this particular instance. But do I gather you would acknowledge the fact that you cannot really have involved consent if the patient is not aware that that is a potential in that particular situation?

Dr. McMAHON. With a child, and with mentally retarded individuals and certain mental diseases, the informed consent should be obtained, of course, from the legal guardians, not the patient.

Mr. WALKER. We're talking here about the researcher. In other words, if the person knew, or at least should have known, and yet it is not a part of the informed consent process because it's not included, then at that point there has been a failure in the system; is that correct?

Dr. McMAHON. It sounds like there was with that cancer drug. I have never heard of such a story and I don't think it occurs. The peer review committees, you know, require a review of the proposed study and the nature of the animal toxicity before they permit a study to go on in most institutions.

Mr. WALKER. Thank you, Mr. Chairman.

Mr. SCHEUER. Dr. McMahon, you say in your testimony that the fundamental methodology for new drug discovery has changed drastically in the last few years, and that we're entering a new molecular biological era.

Dr. McMAHON. Yes, sir.

Mr. SCHEUER. That we don't need codes and guidelines; we need flexibility and commonsense.

Now, we have had this FDA problem for a long, long time. I myself was chairman of another subcommittee of the Science and Technology Committee and requested GAO to give us this report on the decisionmaking process in FDA, and my letter to them was dated May 7, 1977. That's 4 years ago.

I think at that time we were not in the midst of this new molecular biological era. Yet we had a problem then.

Is the urgency that you clearly express on the need to change the system, has that been compounded by this crash-through that we have made into this new molecular biological era?

Dr. McMAHON. That's right.

Mr. SCHEUER. Has the new process of developing drugs—in other words, of really engineering new drugs—made the current system of approving drugs even more chaotic and archaic and dysfunctional than it was in 1977 when I first asked for the investigation?

Dr. McMAHON. I think the system demands some change, just as scientific progress has changed. There are opportunities now we didn't have 4 or 5 years ago. Yes, sir, I would agree with what you say. There is a greater need now to modify the system to permit new developments.

Mr. SCHEUER. Why?

Dr. McMAHON. Because the breakthroughs are potentially there and they're going to be studied abroad if we don't permit them to be studied expeditiously in this country.

I want to be on the record as saying we must not sacrifice patients' safety, but I think institutional peer review committees doing their present thing, doing it now, and the requirements that experts and only a few patients study new drugs, as the system is now, and the requirement that informed consent and patient information about the risks and possible adverse effects, as the system now requires, is a safe system, and I don't think we sacrifice patient protection by changing the system as I recommended.

Mr. SCHEUER. Dr. McMahon, we have had you speaking and answering questions for about 1 hour and 20 minutes. We went terribly, terribly over our time allotment, which bespeaks great, great admiration on the part of all of us up here. It was remarkable testimony and we thank you very much.

Dr. MCMAHON. Thank you.

Mr. SCHEUER. We will now hear from our second witness, Dr. Lewis Sarett, senior vice president of Merck & Co. We have heard from Dr. Sarett before, and he is also a remarkably stimulating professional. We look forward very much to your testimony, Dr. Sarett.

STATEMENT OF LEWIS H. SARETT, SENIOR VICE PRESIDENT FOR SCIENCE AND TECHNOLOGY, MERCK & CO.

Mr. SARETT. Chairman Scheuer, Chairman Gore, and members of the subcommittees, I am Dr. Lewis H. Sarett, senior vice president for science and technology of Merck & Co. It is a pleasure to be here today.

I should perhaps correct the record on the agenda here, which has given me the honor of a medical degree. I am a doctor of chemistry.

Mr. SCHEUER. Dr. Sarett, let me just say that your testimony, extensive as it is, 27 pages, will be printed in full at this point in the record. We are a little bit pressed for time and I would ask you, in a period of 8 or 10 minutes, to sum up the highlights of your testimony, if you would be kind enough to do that, and then I'm sure we'll all have questions for you.

Mr. SARETT. Fine.

My testimony will contain my observations on vaccine innovation, and I define in the written testimony what innovation consists of.

I would note that Merck has long been a leader in the field of immunization and virology. We have a track record in introducing vaccines of which we're very proud.

There are promising opportunities for scientific advances in vaccines. There are lots of challenges to be met and some constraints on our ability to meet those challenges.

I would name those constraints by noting the limited returns on the massive investment required by vaccine innovation that have led to attrition of manufacturers from this field and problems of manufacturer's liability in public health immunization programs. It is apparent the vaccine industry in the United States is not as broadly based as it once was.

Merck, through its technological leadership and its production expertise in this difficult field, has achieved a very powerful position. We are learning every day about the body's immunological system, genetics, bacterial and viral infections, and this basic knowledge does hold tremendous potential for future innovation.

I can be quite specific and mention Merck's research program. We are working on hepatitis A, hepatitis B, herpes simplex 1 and 2, gonorrhea, chickenpox, cytomegalovirus and respiratory virus infections among other things. We have made some breakthroughs in technology which are referred to in more detail in the written text.

The promise of vaccine innovation goes beyond the scientific and medical accomplishments. It goes to social and economic benefits. Historically, immunization has proven its worth in lowered mortality rates and heightened productivity. Moreover, there is the low cost of immunization which results in as much as a lifetime of immunity from a disease which might cost society many billions of dollars to treat.

The State of Massachusetts analyzed its experience over a 10-year period with its measles, mumps, and rubella programs, and they concluded that the citizens of the Commonwealth of Massachusetts saved $12,733,000 over that period. It's a message that preventive medicine really does pay off.

Congress has repeatedly recognized the social and economic value of such immunization efforts by making funding available through the Center for Disease Control for childhood immunization programs for measles, mumps, rubella, diphtheria, whooping cough, tetanus, and polio.

As you know, the U.S. Congress recognized the potential value for the elderly of vaccination programs against pneumococcal pneumonia and passed an amendment to the medicare law to allow reimbursement for vaccinations against this disease. That has had enormous benefits flowing from it, with a predicted 5,000 lives saved in the next 5 years. In the fourth and sixth years, there will be economic benefits showing $6 and $1[illegible] million saved, respectively.

I will pass the statement on hepatitis B or serum hepatitis for shortness of time, not because the disease is not an important one, both medically and economically.

I will turn now to the question of vaccine development and some of the constraints that we have. In the chancy business of biomedical research and development, vaccines are a great gamble. The marketed vaccine product is the result of long and determined persistence of scientific and technical effort, of false starts, and of the researchers' devotion to finding solutions which might lie on the threshold but which might also be many miles down the road.

One example of that in our own laboratories is varicella or chickenpox, which we began research on in 1962, and for which we don't have a practical vaccine even today. On the other hand there is hepatitis B, which we worked on for a number of years, and we do plan to introduce that, with good luck, this coming year.

Another characteristic constraint of vaccine research and development is that a program of public education may be necessary to encourage adults to seek out preventive vaccinations. Vaccination involves convincing healthy people, all of us, adults as well as children, unmotivated by a direct disease experience, to seek a treatment. Healthy adults have no natural compulsion to go and ask their physician to give them a shot or to line up in a clinic. We do need public education if these things are going to work.

The vitality of vaccine research and the introduction of new preventive therapies depend upon the removal of disincentives for those firms which discover, develop and produce vaccine products. The number of vaccine manufacturers has decreased markedly in the United States.

Yet, it is this American industry that, in a way that has not been matched elsewhere in the world, has led the way in developing and producing the many immunizing agents that are now so essential for disease control and prevention. Despite the departure of companies from the vaccine field, our industry is now and should continue to be highly productive and to be the source of new vaccines.

Merck, in contrast to many other major drug companies, has chosen to remain in this field. Today, we are only one of seven indigenous licensed vaccine manufacturers left in the United States. We are one of only four with products left on the market at all, and we are the largest of these as you, Mr. Scheuer, suggested earlier.

As the Office of Technology Assessment has pointed out, in the hard light of business decisionmaking, it appears that for many companies the return on investment in vaccines has not been sufficient to warrant staying in the business. Vaccine discovery, development, and manufacture require a commitment of labor, capital, and resources which yields only slight returns compared to other research opportunities.

Accordingly, renewed strength in vaccine innovation must derive from market forces and policies which generate the expectation of a reasonable return on vaccines. Barriers or constraints are few but potent. Among them are pricing and procurement policies which serve to dampen price increases which might more adequately cover costs, and duty-to-warn and other liability issues. These two difficulties are aggravated by the limitation of a market largely to the United States, because the Government policies of most developed countries restrict our entry to their own home markets.

Because Government purchasing for public health programs accounts for such a large share of the U.S. vaccine market, Federal purchasing policy is a powerful means by which to encourage innovation. Vaccines represent the least expensive form of medicine, preventive medicine, and our least expensive form of health insurance, but their price does not generally reflect their real value. One certain means to provide incentives to the vaccine innovator and to make the vaccine field a more attractive investment would be to recognize that increases in vaccine prices are necessary so that the returns from an innovation are more in line with the magnitude of the investment required.

Compounding the problem of returns on investment is the issue of product liability for vaccines. In recent years this has been a matter of increasing concern for vaccine manufacturers. Questions about the availability of insurance have clouded national immunization efforts, and the liability issue has undoubtedly been a significant element in the decision of some manufacturers to reduce or eliminate their commitment to vaccines.

Several circumstances have contributed to the vaccine liability problem. Although most vaccines are extraordinarily safe, they can be associated with untold reactions in a small proportion of the persons who receive them. As we know, most adverse reactions are limited to a sore arm or a fever for a day or so, pretty minor things, but some rare reactions can be very serious, even fatal.

Seldom, if ever, is anyone at fault when these injuries occur. The vaccine manufacturer can make its products as pure and as safe as

technology permits. The Government can apply the most rigorous standards in approving the vaccine in the first place, and in checking subsequent batches. Public health officials can carefully assess the need for immunization programs, and limit those programs to the segments of the population that are essential to the successful control of communicable disease. Physicians and nurses, in turn, can administer vaccines with the greatest care. Still, when millions of persons are immunized, some will suffer adverse reactions.

Even though no one is at fault, the courts have sought to compensate injured persons by developing novel legal theories. For example, under recent court decisions, a manufacturer that supplies vaccines for use in a public immunization program cannot discharge its legal responsibilities simply by making its product as safe as existing technology permits and warning physicians of any risks that are unavoidable.

The manufacturer is also responsible for assuring that appropriate warnings are communicated directly to persons who receive the vaccine. But the dissemination of information to the public concerning immunization is a function that is ordinarily done by physicians and public health officials. Manufacturers may thus find themselves legally responsible for assuring the adequte performance of functions over which they have little or no control.

Moreover, the publicity that often attends public immunization programs and the unusually large number of persons inoculated can greatly increase the number of claims that are filed. Even if most claims are unfounded, the cost of defending them can be prohibitive. For these reasons, insurers have become increasingly reluctant to cover manufacturers' risks associated with Government-sponscred, mass immunization programs.

There is no easy solution to the vaccine liability problem, but we believe some action must be taken to prevent questions about liability and the availability of insurance from interfering with future immunization efforts. The recent report by the Office of Technology Assessment offers a proposal that deserves careful attention. The OTA report recognizes that injuries caused by vaccine raise special ethical and social questions. Society as a whole benefits when an individual citizen agrees to be immunized against a communicable disease, and if that individual suffers unavoidable injury, the payment of reasonable compensation is a public responsibility. The loss should neither be left with the injured individual nor imposed, through artificial standards of fault, on a manufacturer or physician who has exercised all possible care.

The OTA report recommends a Federal no-fault compensation program to determine whether injuries are vaccine related and to decide the appropriate compensation for injured persons. Many details of the program remain to be worked out. We believe, for example, that it can only work if it supplants the existing fault-based litigation system. But the OTA recommendation is a step in the right direction and should be seriously studied.

Let me emphasize that we have never sought to be relieved of responsibility for making vaccines as pure, potent, and safe as existing technology permits. When we have fulfilled that responsibility and unavoidable injuries result, we believe that some system

other than the tort litigation system should be available to compensate injured persons.

There are other incentives which are being considered which would help to strengthen our vaccine innovation effort in the United States. I would refer briefly to the patent term restoration proposals, which you're familiar with, and other steps.

In conclusion, vaccine discovery and development is an arduous task, requiring a substantial commitment of resources. The value of those labors can be measured in terms of lives made longer and more productive, disease prevented, and health care expenditures averted.

Congress, in its broad consideration of innovation in the vaccine field, and to help assure the vitality of vaccine supply in the years ahead, may want to direct its attention to those areas of vaccine research and manufacture over which the Federal Government has influence or in which it might stimulate innovation.

Thank you.

[The prepared statement of Mr. Sarett follows:]

Statement of Dr. Lewis H. Sarett

I am Dr. Lewis H. Sarett, Senior Vice President for Science and Technology of Merck & Co., Inc. It is a pleasure to be here today.

My testimony will contain my observations on pharmaceutical innovation -- the promises and problems of developing human health vaccines. One must note at the outset that innovation -- in the vaccine field as any other -- is not simply confined to the discovery of a new product. Rather, innovation is the entire process by which a product is discovered and researched, developed and tested, proved effective in clinical trials, produced or manufactured, introduced to the consumer, distributed and serviced.

Merck has long been a leader in immunization and virology. We developed and introduced the first live virus vaccines against measles, mumps and rubella (German measles) and the first combination vaccine for these diseases. We were a pioneer in the introduction of modern vaccines against meningococcal meningitis and pneumococcal pneumonia -- 'Meningovax' in 1974 and 'Pneumovax' in 1978.

We are working on vaccines against hepatitis A and B, herpes simplex 1 and 2, gonorrhea, broad spectrum meningitis and septicemia, varicella-zoster virus (chicken pox-shingles), cytomegalovirus (congenital defect with learning disability), and respiratory virus infections including influenza, para-influenza and respiratory syncytial virus.

Many of the vaccines currently being developed are directed primarily at immunization against diseases of adulthood -- particularly those which are sexually transmitted. The whole area of adult immunization is an approach whose full potential has not yet been realized.

Unquestionably there are promising opportunities for scientific advances in vaccines. There are scientific challenges to be met and some constraints on our ability to meet those challenges. Among these constraints are the limited returns on the massive investment required by the difficult process of vaccine development and problems of manufacturer's liability in public health immunization programs.

It is apparent that the vaccine industry in the United States is not as strong a resource as it once was. The future of domestic vaccine supply depends on the continued willingness and ability of a few companies -- traditionally pharmaceutical companies -- to produce adequate quantities of vaccine and to discover the vaccines of tomorrow.

For the past 39 years, I have worked as a research scientist and then as a research administrator for Merck. Seven of those years were as President of the Merck Sharp & Dohme Research Laboratories. During these four decades, I have witnessed tremendous advances -- made possible by new discovery and broad immunization -- in the prevention of diseases that once killed or maimed whole populations. Polio, diphtheria, smallpox, typhoid, and typhus have all been virtually eliminated in the United States and most of the Western world. Today, millions of children grow to adulthood without ever suffering the once unavoidable measles, mumps, whooping cough, and German measles.

The increase in the average human life span to 73 years was accomplished mainly through the control of infectious disease. In this, vaccines played a major role. Today, we can legitimately view every new

preventive vaccine as a profound potential economic gain as expenditures for hospitalization and medical therapy are rendered unnecessary, as mortality is reduced, and as productivity is increased. Vaccines are a powerful weapon in preventive medicine.

Promises for Vaccine Innovation

Our vaccine research and development efforts are directed toward three objectives: discovering new vaccines for diseases which currently elude immunization, improving existing vaccines, and, from the clues inherent in these discoveries, developing new production processes to serve larger populations.

The search for a new vaccine is commonly built upon the interaction of many different disciplines. These include microbiology, chemistry, biophysics, biochemistry, molecular biology, virology, toxicology, immunology, and bioengineering. New discoveries or approaches in any one of these fields can open new avenues of research to us.

What we are learning every day about the body's immunological system, genetics, bacterial and viral infection, coupled with breakthroughs in such technical processes as recombinant DNA, fermentation, and in vitro growth of bacteria, holds tremendous potential. We look toward a period when new discoveries may come forth more freely and when new production or process innovations will enhance the flow of those discoveries to massive populations.

Perhaps I might address for a moment those innovations which Merck itself sees on the horizon. As I mentioned, Merck is now working on vaccines against hepatitis A, herpes simplex 1 and 2, gonorrhea, chicken pox, and other diseases. These projects are currently in research and development at the Merck Sharp & Dohme Research Laboratory. Dr. Maurice Hilleman, Senior Vice President, Virus & Cell Biology Research of MSDRL, who is an international leader in the development of antiviral vaccines, directs this effort.

In the area of bacterial vaccines, one effort is directed toward protection against gonorrhea. It is feasible to protect against gonorrhea through a subunit vaccine but the optimal vaccine serotype composition has not yet been identified. When appropriate antigens are developed, an effective vaccine will become a reality -- probably by the end of this decade.

Commonly we think of bacterial infections as being treated by antibiotics. However, bacterial vaccines can resolve the problem of reduced antibiotic efficiency because of resistant bacterial strains.

In the area of virus vaccines, we have a number of efforts underway. A human hepatitis B virus vaccine is nearing the end of the development stage and should be introduced next year. The limiting factor in hepatitis B is that the virus will not grow in ordinary cell culture and therefore must be obtained from blood donors who are carriers of the virus. A major breakthrough will come when science develops a means by which to grow the virus in an appropriate cell culture. Merck scientists

made such a breakthrough recently in pursuit of a vaccine against hepatitis A virus.

Early probes are also being made on hepatitis C. Definition of the cause of the disease will be of high priority.

We are currently studying a vaccine for the prevention and treatment of genital herpes that we hope will lead us to an approach for use in other herpes virus infections including varicella; cytomegalo virus; and infectious mononucleosis, naso-pharyngeal carcinoma and African lymphoma that are probably caused by Epstein-Barr virus.

There is potential for developing not only new viral and bacterial vaccines but more broadly efficacious vaccines. This is particularly true in the area of bacterial polysaccharide vaccines. Bacterial vaccines are often composed of the polysaccharide casings of bacteria. By coupling the polysaccharide with proteins, Merck scientists hope to increase the immunogenicity of the polysaccharide vaccine particularly for children under two years of age whose immune systems are not fully developed and for whom such vaccines are less than optimally effective.

In addition to work in these major disease areas and on improvements on existing vaccines, we are constantly seeking innovations in the production processes so vital to the development and mass availability of new vaccines. The cell culture growth of the hepatitis A virus I just mentioned is one breakthrough which will be useful both for the development of the vaccine and the unique production process by which

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it will be made. A second area which holds promise is recombinant DNA. The cloning of bacterial and yeast cells offers hope for eventual vaccine production by alternative and potentially more reliable procedures.

A third area recently pioneered by Merck involves a production technique which will be useful in making large quantities of some types of vaccines -- most notably those for measles, mumps and rubella -- more efficiently. This breakthrough mass production technique is perhaps as significant as Dr. John Ender's discovery that the polio virus could be grown in a test tube and therefore made available for mass immunization. Until several years ago, vaccines were produced in glass bottles, harvested and pooled in large tanks. The glass bottle process was neither efficient nor economic.

In the mass culture technique, initiated at Merck in 1974, production takes place inside a stainless steel tank, stacked inside with discs, containing cells, a nutrient medium, and seed virus. The infected cells stick to the discs and grow. Then, the virus-infected fluid -- the vaccine itself -- is drained from the tank and stored until processed. Today we can produce some vaccines in one or several tanks rather than hundreds of bottles.

The Social and Economic Promise of Vaccine Innovations

The vaccine innovations we see on the horizon will help us more fully realize the social and economic benefits that come from preventive medicine.

Historically, immunization has proven its worth in lowered mortality rates and heightened productivity. Moreover, the relatively minor price of vaccination efforts results in as much as a lifetime of immunity from a disease which might cost society many billions of dollars to treat.

Federal and state governments have widely recognized the social value and economic benefits accruing from immunization programs. By requiring or encouraging that a certain proportion of the population be vaccinated, society seeks to promote the collective good by reducing the chances that the unvaccinated will come in contact with a carrier of the disease.

Childhood immunization programs have long been recognized as a cost effective means by which to achieve society's health goals. There are a number of excellent examples here.

The vaccine to protect against rubella was first tested in 1966 and licensed for wide use in 1969. Childhood immunization began and an epidemic projected for the early 1970s did not materialize. This may have prevented up to 30,000 birth defects among children whose mothers would have been infected during pregnancy. A similar rubella epidemic in 1964-65 resulted in about 20,000 surviving rubella babies in the U.S. who were born handicapped and who require constant care at an eventual cost of over $2 billion, according to estimates of the U.S. Public Health Service.

In 1979, the State of Massachusetts analyzed its experience with its measles, mumps and rubella immunization programs, taking into account the cost of the vaccine program and the actual cost of medical care alone. The Summary Report of the Department of Public Health indicates that between 1966 and 1978, the Massachusetts Measles Immunization Program prevented the occurrence of 205,053 cases of measles and saved the State more than $6,538,722.

The Massachusetts Mumps Immunization Program, between 1969 and 1978, prevented 86,847 people from having the disease and saved the State $1,191,514. The Massachusetts Rubella Immunization Program, between 1970 and 1978, prevented 60,383 cases of German Measles and saved the State over $5,002,960. The Report noted that since 1976, the triviral (measles/mumps/rubella) vaccine has been used exclusively throughout the State, making it possible to immunize against these three diseases in a single visit at a lower cost for the vaccine and administrative expenses. The Report concludes: "Our immunization programs have not only prevented illness and death, but saved the citizens of the Commonwealth of Massachusetts approximately $12,733,196. Preventive medicine does pay off."

Multiply this experience nationally and one can project the potential savings from mandatory or permissive immunization requirements prior to school entry. To this quantitative measure, one must also add a qualitative one -- the elimination of the human suffering associated with these diseases.

Congress has repeatedly recognized the social value of such immunization efforts by making funding available through the Center for Disease Control for childhood immunization programs for measles, mumps, rubella, diphtheria, whooping cough, tetanus, and polio.

Last year, the U.S. Congress, recognizing the potential value for the elderly of vaccination against pneumococcal pneumonia, passed an amendment to the Medicare law to allow reimbursement for vaccinations against this disease. The death rate from pneumococcal pneumonia is 2.5 times higher among those aged 65-74 and 10 times higher for those 75 and over than for the population as a whole. Over 97% of the cost of treating this disease in the elderly is spent on hospital care -- at an average cost of $3,300 per stay. The average per dose cost of the pneumococcal vaccine, including the doctor's fee, is $11.50; vaccination provides protection for up to eight years. According to the Congressional Budget Office, this benefit will save the lives of 5,000 Medicare enrollees in the next five years. Moreover, the benefit will begin producing savings for Medicare within four years. The CBO projects savings of 6 and 11 million dollars in the forth and fifth year.

The importance of public health support of vaccine immunization programs should not be underestimated. As the Office of Technology Assessment has noted, the history of measles immunization indicates that when federal funding of public vaccination is reduced, the incidence of the disease increases.

This is no doubt equally true in adult immunization. Although our experience with this strategy is neither as long-lived nor as well-documented, one can assess the potential of adult immunization in the fact that today the combined mortality from influenza and pneumococcal pneumonia, the two major preventable infectious diseases of adulthood, is significantly greater than all of the preventable childhood diseases put together. We need only look to the history of social and ecomomic benefits of vaccines to project the value of immunization programs from the new vaccines which may be forthcoming.

The economic impact of the diseases on which Merck is now working is substantial. Hepatitis B or serum hepatitis is the most serious of the three currently known viral forms of the disease. An estimated 80-100,000 cases of hepatitis B occur each year in the U.S. causing long-term disability and several thousand deaths. The annual economic impact of the disease in the U.S. is estimated at $650 million. It is exceeded in annual numbers of cases only by gonorrhea, syphilis, chicken pox and mumps. There are an estimated 800,000 hepatitis B carriers in the U.S. and as many as 200 million worldwide who may go on to develop chronic liver disease, cirrhosis or liver cancer.

The social and economic impact of gonorrhea -- which strikes about 985,000 individuals in the U.S. each year -- is likewise substantial.

Vaccines against these diseases and the adult immunization efforts under which they will be administered -- coupled with advances in childhood diseases -- hold the promise of significantly reducing health

care costs, increasing productivity, lowering mortality, and improving the quality of life of millions of individuals.

Yet if the promise of vaccine innovation is to be fulfilled, there are some problems which must be recognized. Vaccine development is a difficult task, at best, requiring sometimes decades of work and enormous investment of resources. The returns on this investment are limited, and consequently, many companies have chosen to opt out of the business. Today, very few companies continue in vaccine innovation and production. Thus, the problems of the industry are two-fold. First, there are the demands of the vaccine development process itself. Second, there are the market forces which, taken together, ultimately discourage investment in vaccines. Perhaps I might shed some light on the nature of these problems.

Problems of Vaccine Development

Vaccine discovery and development is a risky, varied and complex process. Discoveries are often where you find them and even the most promising candidate can be defeated in the latter stages if toxicity is shown in man. In the chancy business of biomedical research, vaccines are a great gamble. The viable vaccine product is the result of long, determined persistence of scientific and technical effort, of false starts, and of the researchers' devotion to finding the solution which might lie just beyond the threshold or far down the road.

Perhaps our experience with several vaccines will best illustrate this point.

First, our experience with one as-yet-unsuccessful vaccine: Varicella - or chicken pox - is a disease of the herpes virus family. The disease itself was first described in pre-medieval times. Up until 1892 it was not differentiated from smallpox, but in 1875, Steiner successfully induced the disease in volunteers.

Merck first began work on varicella in 1962 on a low priority basis because at that time the biological research staff was otherwise committed -- to developing vaccines against measles, mumps and rubella. In 1967, Merck successfully isolated its own strain of the virus. However, it became apparent that varicella was a cell-associated virus, and science had not yet developed a means by which to release the virus from the cell. From 1968 to 1974, the varicella project was deferred -- in part because of technical feasibility and in part due to emphasis on development of live virus vaccines for Marek's disease, a widespread disease of poultry. Working on Marek's disease, also of the herpes virus family, Merck scientists achieved a significant breakthrough when they developed a methodology for releasing the virus from the cell. At this point, development of a varicella vaccine became more feasible. In 1974, the Company began developing vaccine prototypes. Because there is no animal model for varicella, a vaccine virus which would demonstrate immunogenicity (protective properties) and no or minimal virulence (disease causing properties) had to be developed in cell culture.

Scientists have experimented with more than sixty "passages" of virus in cell culture without arriving at the proper balance of properties. Between 1974 and 1980, about ten different vaccines were evaluated in human volunteers. Each of these vaccines took more than 6 months for testing prior to the clinical studies. This work may lead to a vaccine in several years but additional dogged persistence to new approaches may be necessary.

Another -- more successful example -- is Merck's experience with the hepatitis B vaccine which we hope to introduce next year.

Technologically, the development of hepatitis B vaccine was the most difficult challenge we have ever faced. It is the first vaccine ever produced directly from human blood serum and it requires donations of plasma to furnish an ongoing supply. It requires new methods of vaccine preparation, the creation of new measurement criteria, new techniques for the entire production cycle and sophisticated new safety testing methods. Let me describe some of its history.

Type B hepatitis was first recognized about 100 years ago in shipyard workers who developed jaundice after receiving a smallpox vaccine prepared from human lymph. Not until the late 1930s, however, was the link between hepatitis and blood transmission firmly established, when the disease broke out among people innoculated with a yellow fever vaccine which was stabilized by the addition of human serum.

Decades later, in 1964, the hepatitis B surface antigen was isolated by Dr. Baruch Blumberg who won the Nobel Prize for his work.

Blumberg was studying blood factors in different population groups when one of his lab workers, who had been working with the serum of an Australian aborigine, contracted hepatitis B. Then, the hepatitis B virus itself was found. Subsequently, the relationship between the antigen and the virus was demonstrated.

In the early seventies, Dr. Saul Krugman discovered that the hepatitis B virus and surface antigen could be rendered harmless if the human serum containing it were heated, and tests showed that the heated serum was effective in enabling the body to form at least a weak resistance against the disease.

This discovery opened the way for the development of the hepatitis B vaccine, a project which Merck launched in 1968. Early studies at Merck indicated that a highly purified, safe and potent vaccine was possible. When safety and efficacy were proved in chimpanzees, the decision was made to test the vaccine in humans. Results from the first large scale trial of the vaccine by the New York Blood Center showed a near 100% protection against clinical hepatitis with no clinically important side effects from the vaccine. Additional studies are currently being conducted by the New York Blood Center, Massachusetts General Hospital, the U.S. Center for Disease Control, and others.

This clearly is a scientific success story. It appears we have developed a vaccine which is going to be useful in preventing a disease which is widespread and debilitating and which may lead to other more serious conditions. But vaccine innovation, as I noted, is not just the discovery of a new product, however easy or difficult.

Hepatitis B antigen cannot be synthesized or grown in the lab although we hope to be able to do this within this decade. It is found only in the blood of individuals who have had the disease or who carry the disease. Therefore, the first step in vaccine production is to locate -- through the Red Cross or other health agency or clinic -- potential donors in the United States and elsewhere. Each donation enables the protection of about 450 vaccinees.

Once the blood serum is collected, the antigen is extracted and run through a series of physical and chemical processes which purify it.

A large number and variety of tests are carried out to assure the precise content and composition of the vaccine and to ensure the safety and efficacy of the final product, including a 6 month long test in chimpanzees.

Thorough-going testing by the Company and the Bureau of Biologics is necessary every time we make a new batch of the vaccine. The production and testing cycle of hepatitis B vaccine is longer than that for any other vaccine currently in manufacture -- 65 weeks from the input of the plasma to the final release of the packaged vials.

The capital commitment to vaccine manufacture is thus substantial. Hepatitis B will require a facility which is designated for it alone. Normally, vaccine production processes are so varied that even if a facility is used only several months out of a year, it cannot be turned over to another use for the remainder of the year. Merck's influenza facility operates for about 6-8 months out of the year. Its

meningococcal meningitis vaccine facility is in operation 4 months out of the year. This is true for all of the vaccines Merck makes except for measles, mumps and rubella which can be made successively in the same facility.

Not only is vaccine research and development complex, but the production process for viral and bacterial vaccines is substantially different. For instance, the bacterial vaccine for pneumococcal pneumonia consists of 14 polysaccharides -- or 14 different vaccines. These 14 serotypes alone cause over 80% of cases of pneumococcal pneumonia, a disease caused by 83 different types of bacteria. Each of these different types of bacteria produces a chemically unique polymer saccharide capsule that resists the efforts of the body's white blood cells to engulf the bacteria and that can be destroyed only by blood antibodies specific to each type. In pneumococcal pneumonia or other pneumococcal infection, the body takes two weeks to make antibodies against a new polysaccharide by which time the disease is well underway. The vaccine enables the body to develop antibodies that recognize and bind to the bacteria capsules encountered in the disease, making them more vulnerable to the disease fighting mechanism.

The production process for 'Pneumovax' is complex because of the many tests necessary to assure purity. The bacteria are grown first in small culture dishes, then in flasks and tanks of increasing size. When the growth cycle is completed, the bacteria are killed chemically and the polysaccharides are isolated and purified, and finally dried to a white

powder. Since the 14 polysaccharides are chemically different, individual isolation procedures had to be developed for each type. The powder is thoroughly tested to assure that the polysaccharide has the correct chemical composition for the pneumococcal type it represents.

When the dried polysaccharide powders have passed all tests, the 14 types are each weighed, combined in solution, and diluted to the proper quantity. The final solution is again filtered and further tests are conducted to assure identity, purity, and sterility of the finished product. Samples from each lot must be sent to the Bureau of Biologics of the Food and Drug Administration for the Bureau's certification.

It took seven years and about 50 of Merck's most experienced microbiologists, immunologists, biochemists, analytical chemists, chemical engineers, and clinicians to develop 'Pneumovax' -- an accomplishment that scientists had been trying to achieve since 1881, when Louis Pasteur and G. M. Sternberg were the first to isolate the bacteria.

This takes us as far as the development and production of a vaccine. But remembering that innovation also includes the process by which a product is brought to market, I might briefly touch upon this aspect. Vaccines must be shipped nationwide and sometimes internationally at a critical temperature range. Thus, their delivery to the physician and the patient is both more complex and more costly than that for pharmaceuticals. Moreover, to help ensure that society's potential needs are met in the event of an influenza epidemic, vaccine manufacturers produce and supply more vaccine than may be administered in a typical flu

season. Since flu is seasonal and the vaccine strains change annually, manufacturers accept and absorb the cost of vaccines returned when physicians overstock their inventories for epidemics which never arrive.

Secondly, vaccination involves convincing healthy people, unmotivated by a direct disease experience, to seek treatment. They may think their chances of contracting a disease are not enough to warrant vaccination or that if they do contract the disease, it may not be very serious. Healthy adults have no natural compulsion for the prevention of disease; they are mostly interested in a cure and mindful of the number of shots they have to take. The social benefits of preventive medicine are enormous, but a program of public education may be necessary to encourage adults to seek out preventive vaccinations.

Thirdly, vaccine products suffer from self-extinction. There is no repeat business in a life-time vaccine. Thus, the more successful a product is initially, the greater the extent to which its market will disappear over time or be renewable based only on increases in the population.

Policy Problems Affecting Vaccine Innovators

The vitality of vaccine research and the introduction of new preventive therapies depends upon the continued viability of those who discover, develop and produce vaccine products.

The number of vaccine manufacturers has decreased substantially. As noted in a report published by the Comptroller General in June 1980, ten years ago five different firms produced measles vaccine. Today there is only one. At one time there were four manufacturers of rubella vaccine. Today there is only one. Merck is the only domestic manufacturer of measles, mumps, and rubella vaccines. Live polio vaccine is produced by a single manufacturer -- Lederle. Ten years ago four firms produced this vital vaccine.

Yet, it is this industry that -- in a way that has not been matched or even approximated anywhere else in the world -- has played a key role in developing as well as producing the many immunizing agents that are now so essential in disease prevention and control. The industry, working with the National Science Foundation, was a vital factor in developing and producing effective polio vaccines. We at Merck are particularly proud of the work our scientists contributed in the development of live-virus vaccines against measles, mumps, and rubella. Even in the field of influenza, in which the government necessarily must be a first-among-equals in the annual process of creating a formula, this industry has been and remains a prime mover in technological advance. The vigor and performance of the private sector in vaccine development and production has been remarkable.

Merck, in contrast to many other major drug companies, has chosen to remain in the vaccine field. Today, we are one of only seven indigenous licensed vaccine manufacturers left in the U.S. We are one of

four with products currently on the market, and we are the largest of these.

While we are proud of the gains in human health our work has meant, we are nonetheless mindful of the problems involved.

As the Office of Technology Assessment points out, in the hard light of business decision making, it appears that for many companies, the return on investment in vaccines has not been sufficient to warrant staying in the business. Not only is vaccine research reviewed in terms of its promises but in terms of how it compares to the many research opportunities which compete for limited resources.

There are a number of factors which have contributed to low profitability from vaccines and to attrition from the vaccine field. There is the complexity of the innovation process itself. It is an investment which requires commitment of labor, capital and resources which yields slight returns compared to other research opportunities. In 1980, Merck's vaccine research and development activity consumed 134 man years of effort. It required an investment of $15 million, discounting production, distribution, and capital costs. In 1981, this dollar investment will approach $19 million. Yet, in 1980, gross vaccine sales which supported our investment in research and development were only $60 million worldwide. Thus, in a given year, vaccine research and development expenditures are a full 25% of sales.

A 1978 study for the National Science Foundation on the net rates of return on innovations analyzed the benefits accruing to society and to

the innovator from the rubella (German measles) vaccine. The Report estimated that from 1970 to 1976, the rubella vaccine directly resulted in a cost savings to society of $1,163,984,000, in terms of the cost of treating cases that were averted, and that the cost of the immunization programs to administer the vaccine were $25,229,000, a direct net social savings of $1,138,755,000. The report calculated that the internal rate of return to society in cost savings resulting from the rubella vaccine was 150.5 percent. The report found that the innovator -- which happened to be Merck -- invested a total of $17,681,000 (in 1972 dollars) in research and development, capital plant and equipment, and other precommercialization expenses in the period from 1963 to 1969. Between 1970 and 1976, the innovator realized net revenues from the vaccine of $18,745,000. Thus, it was only in the sixth year of marketing the vaccine that the innovator began to pass the break even point. Ultimately, the report calculated, the internal rate of return to the innovator from its product was only 2.6 percent.

We must recognize that adequate returns on the ample investment required by vaccines are essential to innovation. Despite attrition of companies from the vaccine field, industry is now and will continue to be the fountainhead of new vaccines.

Ultimately, stimulus to vaccine innovation must derive from an awareness of market forces and policies which operate against a reasonable return on vaccines. Among these are pricing and procurement policies which serve to dampen price increases which might more adequately cover

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costs, duty-to-warn and other liability issues, and the fact that industry is largely limited to a domestic market because the government policies of most developed countries limit the U.S. industry to its own market.

A measure currently before Congress will serve to stimulate vaccine innovation.

The proposed legislation for patent term restoration includes provision for patents relating to vaccines. It requires your attention and merits your support. It would strengthen the overall research effort in this field by providing a more adequate return on the investment made in developing a new vaccine.

In terms of government programs already in place, I might make several comments. The federal government has offered some assistance in addressing one aspect of this problem. Funding through the National Institute of Allergic and Infectious Diseases has stimulated vaccine research and, as the Office of Technology Assessment has noted, may be meaningful in the development of so-called minority vaccines -- those needed for relatively rare conditions or small populations.

Because government purchasing for public health programs accounts for such a large share of the vaccine market, federal purchasing policy is a potentially powerful means by which to encourage innovation. There are several approaches by which purchasing policy might be used to reward the vaccine innovator. Vaccines represent the least expensive form of medicine -- preventive medicine -- and our least expensive form of health insurance, but their price does not generally reflect the real value they represent. One means, certainly, to provide incentives to the vaccine

innovator and to make the vaccine field a more attractive investment would be to recognize that increases in vaccine prices are necessary so that the returns from an innovation are more in line with the magnitude of the investment required for that innovation.

Compounding the problem of inadequate returns on investment is the issue of product liability for vaccines. In recent years, this has been a matter of increasing concern for vaccine manufacturers, Questions about the availability of insurance have clouded national immunization efforts, and the liability issue has undoubtedly been a highly significant element in the decision of some manufacturers to reduce or eliminate their commitment to vaccines.

A number of factors appear to have contributed to the vaccine liability problem. Although most vaccines are extraordinarily safe, they can be associated with untoward reactions in a small proportion of the persons who receive them. Most adverse reactions associated with vaccines are minor and self-limiting -- a sore arm, for example, or a slight fever. But some rare reactions can be very serious, even fatal.

Seldom, if ever, is anyone at fault when these injuries occur. The vaccine manufacturer can make its products as pure and safe as modern technology permits. The government can apply the most rigorous standards in approving new vaccines and in testing individual batches of vaccines before they are released. Public health officials can carefully assess the need for immunization programs, and limit those programs to the

segments of the population that are essential to the successful control of communicable disease. Physicians and nurses can administer vaccines with the greatest care. Still, when millions of persons are immunized, some will suffer adverse reactions.

Even though no one is at fault, the courts have sought to compensate injured persons by developing novel legal theories. For example, under recent court decisions, a manufacturer that supplies vaccines for use in a public immunization program cannot discharge its legal responsibilities simply by making its product as safe as existing technology permits and warning physicians of any risks that are unavoidable. The manufacturer is also responsible for assuring that appropriate warnings are communicated directly to persons who receive the vaccine. But the dissemination of information to the public concerning immunizations is a function that is ordinarily performed by physicians and public health officials. Manufacturers may thus find themselves legally responsible for assuring the adequate performance of functions over which they have little or no control.

Moreover, the publicity that often attends public immunization programs and the unusually large number of persons inoculated can greatly increase the number of claims that are filed. Even if most claims are unfounded, the cost of defending them can be prohibitive. For these reasons, insurers have become increasingly reluctant to cover manufacturers' risks associated with government-sponsored mass-immunization programs.

There is no easy solution to the vaccine liability problem, but we believe some action must be taken to prevent questions about liability and the availability of insurance from interfering with immunization efforts in the future. The recent report by the Office of Technology Assessment on Compensation for Vaccine-Related Injuries offers a proposal that deserves careful attention. The OTA report recognizes that injuries caused by vaccines raise special ethical and social questions. Society as a whole benefits when an individual citizen agrees to be immunized against a communicable disease, and if that individual suffers unavoidable injury, the payment of reasonable compensation is a public responsibility. The loss should neither be left with the injured individual nor imposed, through artificial standards of fault, on a manufacturer or physician who has exercised all possible care. The OTA report recommends a federal no-fault compensation program to determine whether injuries are vaccine-related and to decide the appropriate compensation for injured persons. Many details of the program remain to be worked out; we believe, for example, that it can only work if it supplants the existing fault-based litigation system. But the OTA recommendation is a step in the right direction and should be seriously studied.

Let me emphasize that we have never sought to be relieved of responsibility for making vaccines as pure, potent, and safe as existing technology permits. When we have fulfilled that responsibility and unavoidable injuries result, we believe that some system other than the tort ligitation system should be available to compensate injured persons.

Conclusion

In the United States we will have to view the vaccine industry -- as other nations have -- as a national resource. Vaccine discovery and development is an arduous task, requiring a substantial commitment of resources. The value of those labors -- and their ultimate promise -- can be measured in terms of lives made longer and more productive, disease prevented and health care expenditures averted.

It appears that policy attention may be necessary to insure that the rewards for successful development of vaccines provided by the free enterprise system are adequate to insure the vitality of the industry and the adequate flow of new vaccine products. Congress, in its broad consideration of innovation in the vaccine field and to help assure the vitality of vaccine supply in the years ahead, may want to direct its attention to those areas of vaccine research and manufacture over which the federal government has influence or in which it might stimulate innovation.

Mr. SCHEUER. Thank you very much, Dr. Sarett.

When I referred to your seeming monopoly in the field before, I meant that tinged with admiration and great respect, that your company was a survivor and was not one of those who dropped by the wayside.

Is your dominant position today due to the fact that you have been able to operate profitably in this field while others weren't, or is it that your activities in the vaccine field show a modest profit or no profit and are supported, in effect, by other more lucrative and more profitable activities outside of the vaccine field?

Mr. SARETT. That segment of our business which involves vaccines is relatively unprofitable. We have been a leader in the field, I think primarily because our research and development effort has been led by an extraordinary man and by an extraordinary group of researchers that he has put together. Finding ourselves, technologically, in the leadership, we have brought other phases of technological innovation to the same level of expertise. We are very proud, also, of our manufacturing capabilities. We feel, in general, our public education efforts in this field are excellent.

In spite of the relative lack of profitability, we are faced with a technically successful operation which also carries with it a heavy social responsibility. We are very mindful of that responsibility.

Mr. SCHEUER. Is this activity of yours, this remarkable program, in the field of vaccines really supported by more profitable pharmaceutical lines which your company carries?

Mr. SARETT. We don't break out the profit and loss in that amount of detail. As you know, it's very complicated.

But it certainly would be, if you wanted to characterize it loosely, it would be a break-even proposition.

Mr. SCHEUER. Well, the payoff to society, as you expressed it, is enormous. On page 9 you talk about an $11.50 vaccine cost to the Government, avoiding hospital care at a cost of $3,300 per stay. That has to have a spectacular cost-benefit factor. And on page 21 you talk about a savings to society of $1.164 billion, at a cost of slightly over $25 million, a net savings to society of over $1.1 billion. That has to be a spectacular return to society and there ought to be some way that society can make it at least moderately profitable to you.

Could some system be devised—and you talked about increasing your sales price to mostly Government purchases, I take it. Is it conceivable that you could work out a system that would provide, let's say, a somewhat higher price during the early years of use? I think you mentioned somewhere in here that it took 6 years to get back your investment on a particular drug before you began to make a profit. That's an awful long time for a business firm in this country. It might not be in Japan where they have a different kind of——

Mr. SARETT. Yes.

Mr. SCHEUER. It's a long time in this country.

Do you believe that it might be possible to work out some kind of a fee schedule which would give you a substantially higher price for your product while you were still in the process of regaining your initial investment, plus interest, and perhaps when you recovered your investment plus interest, and you're in a profit now and

drawing a cash flow that is profitable, that that high price might be reduced somewhere.

In other words, you would have an initial period that would get you back your investment, perhaps in 2 or 3 years rather than 6 years, at, let's say, double the price, and after that it would come back to some kind of less expensive price to the Government, on the assumption that this was now profit and you had gotten back your net, so to speak.

Is it conceivable that an arrangement of that kind could be worked out?

Mr. SARETT. I think you are describing the way that we would all hope that normal market forces would work, because after a drug has been introduced, competitive pricing pressures usually come into the picture in 4, 5, 6, or 7 years, with a slightly better version or a cheaper version, perhaps, providing only that the incentives to keep other manufacturers in the field are there. As long as we don't make the disincentives so persuasive that one company alone is left—I think those things will happen.

Mr. SCHEUER. I agree with you. It's not a healthy situation for our country. Either you're the only survivor due to a certain sense of benevolence and public responsibility—in that you're willing to carry a drug for years and years on essentially a break-even basis—or you're more clever than the others and under these difficult conditions you're able to make a profit where the other companies dropped by the wayside because they weren't quite as innovative as you. From the society's point of view, that's not a good situation.

Let me ask you, in Europe, let's say, does this same situation prevail, with just one or two vaccine manufacturers per country, or does the economic framework over there make it possible for more entrepreneurs to get into the vaccine development business and make a reasonable profit?

Mr. SARETT. No, you would find in Europe, the socialized medical system that they support over there has gone to the extreme case for vaccines. Uniformly, they have a national serum institute or a national vaccine institute which is wholly supported by the government and its tax system, so there is only one source of vaccines administered and produced by the government.

Mr. SCHEUER. And how has that system managed in terms of innovative creation of new drugs compared to our own system, where there are at least three or four left?

Mr. SARETT. I think it has lagged well behind us in terms of innovation. The great majority of new vaccines come from the system that we have here in the United States.

Mr. SCHEUER. Well, Dr. Sarett, we very much enjoyed your testimony. I have a number of other questions that I will probably send you in the mail.

From here on, we're all operating under the 5-minute rule. I will defer to my colleague, Congressman Gore.

Mr. GORE. Thank you very much. I will be very brief.

You make the vaccine for measles, is that correct?

Mr. SARETT. Yes, sir.

Mr. GORE. There was a report just in the last couple of days that measles may be completely eliminated by the end of 1982. Do you agree with that prediction?

Mr. SARETT. You're quoting Dr. Allan Bloch, I think, of the Communicable Disease Center——

Mr. GORE. Right.

Mr. SARETT [continuing]. And the numbers that he gave were remarkable. He's the expert, of course, and all I can say is, if he said it, then I believe it. Of course, I don't know what you're leading up to, but it is kind of like the good news and the bad news. [Laughter.]

The good news is that we have cured measles; the bad news is, we don't have a product any more.

Mr. GORE. I guess that's right. But it's quite a blessing for the American people——

Mr. SARETT. That's what it's all about, really.

Mr. GORE. I hope so. I hope so.

Of course, you don't tell your stockholders that always, do you?

Mr. SARETT. Well, it's like peeling away layers of an onion, isn't it? When measles is gone, there will be other diseases, such as I mentioned in my written testimony.

Mr. SCHEUER. If my colleague will yield, I suppose even your hardhearted stockholders take a little pleasure and satisfaction in having worked themselves out of a market due to the spectacular success of their efforts.

Mr. SARETT. Many of the stockholders are parents of little kids, and I am sure they would be very glad to have that tradeoff.

Mr. CARNEY. Would my colleague yield for a clarification on that?

Mr. GORE. Sure.

Mr. CARNEY. Thank you, Mr. Gore.

I was just wondering, we consider smallpox as being eradicated in the United States, but only because each and every child born in the United States receives a vaccination; is that correct?

Mr. SARETT. There was sufficient herd immunity developed, enough percentage of the population was vaccinated. In the case of smallpox, it would have been just about everyone, yes. So that it was eradicated.

You don't have to vaccinate every single person to eradicate a disease.

Mr. CARNEY. But do we do that in the case of smallpox here in the United States?

Mr. SARETT. Measles?

Mr. CARNEY. Smallpox.

Mr. SARETT. We did have a vaccination program for smallpox in the United States; yes.

Mr. CARNEY. Is it not true that you can't enter a public school without being vaccinated for smallpox?

Mr. SARETT. Today I'm not sure that that's true. It certainly was true.

Mr. CARNEY. My point being, I'm not so sure that the great news is that we've eliminated measles. That's maybe if we have a public health program that requires everyone to receive the vaccination.

Mr. SARETT. Oh, your point is very well taken, surely. I think that's why Dr. Bloch was pointing out how good the immunization program is and how effective, and the hope that next year they'll be able to reduce those numbers still further and then eradicate it.

Mr. CARNEY. You used the term "herd" immunization?

Mr. SARETT. Herd immunization, yes, h-e-r-d.

Mr. CARNEY. In other words, the masses are so that the chance of that disease to spread to a new generation are slim or none at all?

Mr. SARETT. Exactly.

Mr. CARNEY. Now, would that measles problem be worldwide or confined to, say, the Western Hemisphere or whatever?

Mr. SARETT. He was speaking, I think, of the United States and the eradication of measles in the United States.

Elsewhere in the world, it can be a severe problem.

Mr. CARNEY. Then I would suspect they will still be giving measles vaccine to everyone in the United States long after 1982, although the good news is we doubt anybody will catch it.

Mr. SARETT. Yes.

Mr. CARNEY. Good news for your stockholders and good news for the United States.

Thank you, Mr. Gore.

Mr. GORE. Yes, thank you.

It is, indeed, a blessing we can look forward to with the elimination of that disease.

Can you cite any others that you think are now within reach for elimination, in addition to smallpox and measles?

Mr. SARETT. Well, in the United States typhoid fever has become quite rare. That has resulted from better hygiene practices. That's a disease, a Salmonella-like disease, that is carried by infected water supplies, and our water supplies are infected less and less by waste contamination. That is a good candidate, I would say. Although elsewhere in the world, of course, it will go on for decades.

Mr. GORE. Well, we are certainly grateful to companies like yours who are willing to work on projects like this, in spite of the fact that you're well aware that you're working toward the elimination of that market.

Now, with respect to an individual who dies or is injured, through no fault of his own, by his reaction to the vaccine, who do you believe should bear that loss?

Mr. SARETT. I believe that it's a Federal responsibility because of the fact that when an individual is vaccinated, he is not only doing that for the benefit of his own health, he is contributing to the health of society through the herd-immunization process that we were talking about a moment ago. In other words, if you go and roll up your sleeve and are vaccinated, you may, being immune, prevent your associates from catching that disease, or I may prevent you from catching that disease. So we are making a contribution to society at large.

Mr. GORE. I understand that. But you have a problem then of removing some of the incentive to guard extra diligently against any safety problem and, second, that ignores the fact that some substantial benefit still does go to the company. I wouldn't want the record to reflect that you are, in fact, cross-subsidizing vaccines so much that you're not making any money on it. You are, in fact,

making some return and should assume some of the risk, at least that's what I would conclude.

Don't you think you should assume some of the risk?

Mr. SARETT. Well, the company assumes all of the risks that are involved in negligence or in improperly manufactured vaccines. That risk is always present.

Mr. GORE. But you said a moment ago that you think the society as a whole should assume all of that risk.

Mr. SARETT. Oh, I failed to distinguish.

Mr. GORE. OK.

Mr. SARETT. In the case where the vaccine has been manufactured properly, has been administered properly, has been approved by the Federal Government through the Bureau of Biologics properly, there is no fault, and yet when someone is injured and he contributed his vaccination, so to speak, then I think the Federal Government should compensate him.

Mr. GORE. What you're saying, as I interpret it—and correct me if I'm wrong—is that your principal complaint or problem these days is with the liability laws and far less so with FDA; is that a fair summation?

Mr. SARETT. That's correct.

Mr. GORE. OK.

Thank you, Mr. Chairman.

Mr. SCHEUER. Mr. Carney.

Mr. CARNEY. Thank you, Mr. Chairman. I would just like to ask a couple of quick questions, keeping in mind the time. Mr. Sarett, if you would keep your answers short I would appreciate it.

One, are vaccine manufacturers so few in number in European countries?

Mr. SARETT. Yes, about one per country.

Mr. CARNEY. And two, taking all the money that you spend in your vaccine and pharmaceutical operation, could you give me an idea of how much is being spent to produce already proven vaccines for the market, as opposed to how much money is being spent for R. & D. on new vaccines?

Mr. SARETT. It would be difficult to break that down because each vaccine is a different problem. The production of hepatitis B vaccine, there is so much involved and it's such a lengthy process—it takes about 1 year—that the manufacturing operation is very expensive. Some vaccines have lengthy research programs; others have much shorter ones and less expensive ones. So a comparison of that is something that I would have to analyze.

I can say this much, however. The percentage of R. & D. sales in our vaccine program is much higher than in our pharmaceutical program. In other words, we put out an awful lot of money in research and development compared to the very limited sales that we have in the vaccine field.

Mr. CARNEY. Could you provide that for us at a later date? Could your company provide that?

Mr. SARETT. I think we could do that.

Mr. CARNEY. A later date means as quickly as possible, OK?

Mr. SCHEUER. We're going to hold the record open for 10 or 12 days, or 2 weeks, and if you could get it to us within that time, we would appreciate it very much.

If you can't and need another few days, just ask us and we'll hold the record open.

Mr. SARETT. We will do that.

[The following was subsequently received for the record:]

VACCINE RESEARCH AND DEVELOPMENT EXPENDITURES AS A PERCENTAGE OF VACCINE SALES

In 1980, Merck's vaccine research and development activity required an investment of $15 million, discounting production, distribution, and any capital costs. The Company's vaccine sales in that year amounted to $60 million worldwide. Thus, in a given year, vaccine research and development expenditures were a full 25 percent of sales. To look at it another way, vaccine research and development funds come from vaccine sales revenues already earned. In 1981, Merck projects that it will spend about $19 million in vaccine research and development. Thus, the Company is currently reinvesting about 32 percent of vaccine sales revenues in research and development.

This is a substantial commitment, even in a research-intensive industry. To illustrate its order of magnitude, one might note that overall, on averge, U.S. pharmaceutical companies spend six percent of their total sales on research and development, compared to about two percent for industry as a whole.

Mr. CARNEY. My next question is, The vaccines are basically used for communicable diseases, correct?

Mr. SARETT. Right.

Mr. CARNEY. Right now in the United States, what communicable disease would you like to have a vaccine available for to prevent that spread? What is the most crucial communicable disease as you see it that we should apply a new vaccine to?

Mr. SARETT. Going beyond the ones that are available today?

Mr. CARNEY. That's correct.

Mr. SARETT. There are two of them that I think are terribly important—there are many of them that are important, but two come to mind right away. One of them is hepatitis B, because hepatitis is such a serious disease, and secondly, I would say cytomegalo virus, which is a virus which affects pregnant women and deforms their offspring, so that their infants are born in a high percentage of cases with deformities, comparable to German measles, except that it's a more severe problem.

Mr. SCHEUER. If my colleague will yield——

Mr. CARNEY. I would be glad to, Mr. Chairman.

Mr. SCHEUER. Wouldn't you also add the sexually transmitted diseases, herpes and gonorrhea?

Mr. SARETT. I certainly would. Those are very serious problems.

Mr. SCHEUER. We seem to have an absolute explosion, an epidemic explosion, of these serious sexually transmitted diseases.

Mr. SARETT. I absolutely agree, especially with the herpes simplex No. 2 virus. Gonorrhea, of course, we would love to have a vaccine for, although there are, after all, antibiotics available. As for the cytomegalo virus—there is no antibiotic that will cure a deformed child. That's why I put that in and omitted, in answer to your question, gonorrhea.

But the sexually transmitted viral diseases are a growing problem. There is no treatment for them. They lead to desperate situations. We very much need vaccines for these diseases.

Mr. CARNEY. I have one last question.

Mr. SCHEUER. Go ahead.

Mr. CARNEY. I have one last question, and I don't mean this to be a bombshell, but I think it's an important question.

There are many viruses that could be utilized in bacteriological warfare. Are you aware of any program to stockpile viruses in case this type of activity is brought about by an adversary of our Nation?

Mr. SARETT. No, sir, I'm not.

Mr. CARNEY. I was just wondering if there was anyone in this room who might be available to answer that question, who would have any more expertise or knowledge—I shouldn't say expertise, Dr. Sarett—of that question, and if they do, they certainly can come forward. I don't think the chairman would have any problem.

Mr. SARETT. I'm afraid my responsibilities are more to heal people, to develop drugs and vaccines, and the use of these agents for warfare purposes is just outside of my——

Mr. CARNEY. Well, that's for healing people, though. We're using it to heal people who might be subjected to a virus because of an antagonistic move against the United States.

Mr. SARETT. I don't know of any such thing.

Mr. CARNEY. Thank you, doctor.

Thank you, Mr. Chairman.

Mr. SCHEUER. Thank you, Bill.

Doctor, just in closing, on page 10—I misread your testimony. I read it very carefully and was tremendously impressed by it. But when you said, "The social and economic impact of gonorrhea, which strikes about 985,000 individuals in the United States each year, is likewise substantial," and that "vaccines against these diseases and the adult immunization efforts under which they will be administered hold the promise of significantly reducing health-care costs, increasing productivity, lowering mortality, and improving the quality of life of millions of individuals," I read that to believe that our country or your firm was on the brink of a real breakthrough in the development of a vaccine directed toward these sexually transmitted diseases, gonorrhea and herpes.

I take it we aren't close to that breakthrough, or are we?

Mr. SARETT. I would say, with respect to the typing of different strains of gonococcus, we are where we were 6, or 7, or 8 years ago with meningococcus and pneumococcus. The problem doesn't seem overwhelming, but there's a lot yet to be done. I think probably the chances are better than even that before the decade is through we will have a vaccine for gonorrhea.

Mr. SCHEUER. And herpes?

Mr. SARETT. I hope herpes.

Mr. SCHEUER. Is there anything the Congress could do to implement that effort and to fortify it and perhaps reduce the time it takes to develop it? These are major national health problems.

Mr. SARETT. They are.

The tremendous support, of course, which is given through the NIH to basic research in this field must be kept up, because the breakthroughs will come there and the industry will I think stand ready to develop a vaccine as soon as that basic knowledge is there. We are starting to move into the field now.

If you look back again at the career of Robert Austrian on pneumococcus, he studied the pneumococcus for his entire professional

career. We need a few dedicated people like that in the biomedical research community to do that with these other viruses you refer to.

Mr. SCHEUER. How long will it take before the federally supported basic research is done through NIH, before the pharmacological firms like yours can get on to the practical development of the vaccine?

Mr. SARETT. Well, we are at a stage where it's more difficult for me to make predictions about herpes No. 2 than it is about the gonococcus. It's a more difficult virus. It is one which is perhaps not so immunogenic. The natural history of the herpes No. 2 disease shows that you don't really develop very good immunity to a natural infection, and it may be that the vaccine that is made will not be immunogenic enough. So that a higher degree of antigenicity will have to be built into it, or an adjuvant will be needed to go with the vaccine. So you can foresee some problems. I wish I could put a number of years on the prospects, but I really can't in the case of that one.

Mr. CARNEY. Mr. Chairman, I would just like to make one clarification. My counsel indicated to me that I might have seemed to have referred to the stockpiling of viruses as a means of offensive warfare. I was generally referring to the stockpiling of vaccine as an antidote, or as a means to prevent biological warfare.

Is that how you understood my question before?

Mr. SARETT. No; I misunderstood your question first, and then you clarified it, and now I understand what you're saying.

Mr. CARNEY. What I meant to say was that I have some concern that that could happen. My concern is this: Are we stockpiling vaccines so we can react defensively to that type of activity, and if we are not, how long do you think it would take the pharmacology industry to gear up to react to something like that?

Mr. SARETT. I'm afraid that question would have to go to the Department of Defense. To my knowledge, corporations are not involved in stockpiling of vaccines against viruses which might be used in warfare.

Mr. CARNEY. OK. Thank you. I just wanted to make that clear. It would be a terrible misunderstanding if anybody thought I had been referring to the stockpiling of virus for offensive purposes.

Mr. SARETT. I appreciate that.

Mr. SCHEUER. Dr. Sarett, as predictable, you have been a very thoughtful and very stimulating witness. Thank you very, very much.

Mr. SARETT. Thank you.

Mr. SCHEUER. We now have three panels, one on neuropsychopharmacology, one on cardiac drugs, and one on prostaglandins.

We will call the panel on neuropsychopharmacology, Dr. Floyd Bloom of the Salk Institute, and Dr. Frederick Goodwin of the National Institute of Mental Health. We are very happy to have you both.

Why don't we proceed with Dr. Bloom first, and then Dr. Goodwin, and then the panel will be asked questions.

Dr. BLOOM. Thank you, Mr. Chairman.

Mr. SCHEUER. We have your testimony and we've had a chance to read it, both of you, and both statements will be printed in full in the record. So I suggest you each take about 7 or 8 minutes, simply chatting with us informally, and then we'll have questions.

STATEMENTS OF DR. FLOYD E. BLOOM, M.D., SALK INSTITUTE; AND FREDERICK GOODWIN, M.D., NATIONAL INSTITUTE OF MENTAL HEALTH

Dr. BLOOM. I will try to be very brief, and just say that we feel it's a very optimistic period of time in the development of drugs that affect specific mental and behavioral problems. Because of the discovery of so many new neurotransmitters in the brain, we have a tremendous opportunity to understand the way in which the logical development of drugs may take place to selectively alleviate important problems.

The three that I was asked to address were drugs to treat pain, drugs to treat depression, and drugs to treat anxiety.

We are very optimistic in the category of treating pain because the basic underlying systems of the brain that allow us to respond to painful stimuli are very well understood, and so the way in which we can use drug molecules selectively to treat pain is an outstanding area for important development. In almost every issue of our journals these days, one leans to yet another natural compound that may be involved in a way to treat pain in an effective way.

If we move from the area of pain to the area of an important mental illness like depression, although we have some very effective drugs and although they are the result of a lot of research efforts, our ability to understand what's wrong in a patient who is depressed is much, much less than our understanding of what is going on in our brains when we hurt; therefore, the ability to provide specific and logical drug molecules for depression requires some sort of intermediate test. These intermediate tests are often based on animal responses to drugs that alter their behavior in ways that we think will help us predict whether, when it's carried to man, those drugs will also be antidepressant in nature.

Of the three states on which you asked me to make testimony, the treatment of anxiety is perhaps the one in which we have the largest area of unknowns. We have a couple of families of drug compounds that are very effective in treating anxiety, and some strong suspicions that one might be able to understand how and where in the brain those drugs act. But the actual nature of anxiety—and there are several kinds of anxiety that are known to exist and adversely affect people in large numbers—that's very difficult to be sure of and, therefore, drug development tends to be a kind of accidental process when, without knowing what you're looking for, you happen to find something that as an unexpected side effect can be exploited to develop drugs that are very selective.

The previous testimonies have also illuminated some aspects that are important to keep in mind when considering the new drugs that will be released as a result of the discovery of new neurotransmitter molecules. Many of the new compounds are really naturally occurring substances that our brain already makes. Our brain makes a very powerful series of molecules and that is the normal

way in which we suppress the response to pain. Making those molecules available as drugs is quite different than trying to discover a way to make a new kind of morphine that is nonaddictive.

In this case we are really giving back to people the natural molecule that they would normally make, perhaps giving it to them in larger amounts or in chemical analogs that are more resistant to being broken down by the body. But it's important in the sense it's not a drug, it is a natural compound, very much like insulin is for the treatment of diabetes. The amounts that are necessary to produce a very significant behavioral effect in man are extremely low, perhaps a millionfold less than an aspirin tablet, for example, so that the current ways of testing for drug toxicity when it's based on a natural product have to be revised and have to be looked at in a very flexible manner in order to make these new compounds available to people with a minimum amount of delay time.

Those are the general points I would like to make, Mr. Chairman. I think it would be better if I stopped and have you ask me questions.

[The prepared statement of Dr. Bloom follows:]

Prepared Testimony

by

Floyd E. Bloom, M.D.

for the Committee on Science and Technology

U.S. House of Representatives

Sub-Committees on Natural Resources, Agriculture Research and

Environment, and Investigations and Oversight

Hearings on "Pharmaceutical Innovation: Promise and Problems"

Monday April 27, 1981

Mr. Chairman, as a physician and a neuroscientist trained in the analysis of drugs acting on the brain, I am pleased to appear before this joint Sub-Committee meeting and provide my testimony on the subject of neuropsychopharmacology. By way of brief description of my background, I am a member of the National Academy of Sciences, and serve as Chairman of the Neurobiology Section. I have been a member of the National Advisory Mental Health Council, and the Research Task Force of the President's Commission on Mental Health, and I have recently been appointed a Member of the National Commission on Alcoholism and Alcohol Related Problems, although that Commission has not yet become operational. I work at the Salk Institute where I am a Research Professor and Scientific Director of the Alcohol Research Center.

Your staff has indicated you are specifically interested on developments which may lead to new drugs for the treatment of pain, anxiety

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and depression, and I will therefore limit my remarks to these problems. These three problem areas represent important practical problem areas, and allow me to address the key elements in drug development, as well as current problems.

Pain-killing drugs are an excellent starting point. Pain is one of the major reasons why patients consult their physicians, and a very large number of different types of anti-pain drugs have been made available. However, an effective approach to the treatment of pain requires not only the determination of the source, severity and frequency of the painful stimulus, but also that the physician assess that individual patient's response to the pain in order to select the optimal treatments. Although narcotic analgesic drugs, such as morphine and synthetic opiates, are widely used and effective drugs for the treatment of severe short term pain, the important problems of drug dependence and addiction limit their usefulness in chronic pain conditions. Non-narcotic analgesic drugs, such as the classical aspirin, and the newer "super aspirin-type" drugs, are much more useful for chronic types of mild pain when they arise from specific local sources (such as headaches, arthritis, and menstrual cramps) but these drugs may also be very difficult to tolerate on chronic use because of their side effects on the gastro-intestinal system or other contra-indications in the patient's history. There is a very real need for effective, non-addictive pain medications which are tolerable without the dangers of drug dependence and which can be used both in acute and chronic pain conditions. The area of the treatment of pain is a very hopeful one, in which there have been important scientific advances, and in which there

is tremendous opportunity for rational drug development.

The reasons behind this optimism are several. First, fundamental studies done over several years have successfully demonstrated the precise nerve channels through which painful stimuli are transmitted into the nervous system, and carried upwards from the level of the primary and secondary relays in the spinal cord and brain stem, to reach the higher levels of brain function responsible for the conscious perception of pain. Normally, the body responds to sudden painful stimuli by immediate reflex withdrawal from the injuring event (a sharp edge or a hot surface) even before we are aware that we are hurt. Second, more recent studies have helped provide a means to understand why it is that we can consciously suppress the intensity of some pains, and why some of us can do this, either by genetic endowment, will power or learning, more successfully than others. This ability depends on the fact that the brain has circuits whose function it is to alter the perception of pain. The maps of these circuits are also fairly well determined, and the neurotransmitters responsible for this pain suppression function are well on their way to identification. Several classes of natural chemicals, that is, substances made by our brains, have the incredible ability to suppress pain perception. The most powerful of these substances are the endorphins, whose name means "endogenous morphine." These chemicals are small peptides which are produced at several places in the brain and in other peripheral nerve cells and endocrine glands, and when given to patients or animals are able to provide all of the pain relieving actions of morphine-like drugs. Although they were only identified a few years ago, there has already been a very

large effort by pharmaceutical development teams in academic and industrial labs to develop analogs of the these natural peptides with more potent actions than those produced by our bodies, as well as alternative means to encourage the body to release more of its own endorphins under conditions of pain.

Because the anatomy of these pain-suppressing brain circuits are known, it has already proven very beneficial in certain patients suffering with very severe forms of chronic pain to be treated by the insertion of stimulating electrodes directly into these brain circuits, and to allow the patients to activate these circuits through externally controlled stimulators. This extreme procedure in some patients can permit good pain relief without drugs and is available on demand, without addiction, and often usable for many months. In addition, synthetic versions of natural endorphin have already been given to human subjects in other countries, such as Japan, by direct introduction into the membranes around the spinal cord to reduce acute and chronic severe pain ranging from the pain associated with childbirth to that of severe metastatic cancers. These treatments seem to provide pain relief of many hours duration without the problems of suppressing the consciousness of the patient, or the newborn child. We might note that such clinical research experiments are more-or-less impossible to do in the U.S.A. because of our regulatory rules. Analogs of endorphins are also being sought which may provide effective pain relief without the necessity for direct introduction into the nervous system. Scientific research has also revealed other novel natural transmitter chemicals with the ability to suppress responsiveness

to painful stimuli in animals, and these are undoubtedly being pursued now for forms whih may be marketable medications. All of these practical developments are areas of intense current research, made possible from years of laboratory research which has determined the methods for tracing brain circuits, determining how connected nerve cells transmit information to each other by chemical message, and how drug molecules may be developed out of chemical variations in natural molecules or by interfering with the special biological properties of specific nerve cells (see Figure attached).

When we turn our attention from drugs which treat pain to the other two categories on which you are now seeking testimony, the scientific situation for drug development opportunities is somewhat different. I shall defer to Dr. Goodwin's testimony for more accurate definitions of these important psychiatric conditions which affect literally millions of our citizens every year, and which can be as incapacitating as the pain states we have just discussed. In fact, it is almost certainly the case that the number of days of productive living lost as a result of incapacitating depression or anxiety exceeds the burden of illness associated with those pain-states. However, in the case of anxiety and depression, scientists do not yet understand what is wrong among the brain circuits or known neurotransmitters which in these unfortunate patients results in anxiety or depression. These two separate behavioral conditions, anxiety and depression, may well be a root cause of some forms of drug abuse as well. In the views of many behavioral pharmacologists, the abuse of alcoholic beverages can be linked to attempts to use alcohol

as a self-administered widely available drug which under some conditions can calm the anxious person and briefly elevate the spirits of the depressed. Because we do not yet recognize what neuronal circuits are overactive or underactive in either anxiety or depression, nor what the transmitters are in these still unrecognized, but behaviorally important circuits, it has not yet been possible to enter the era of logical drug development which we have recently gained with pain medications. Nevertheless, the development of antidepressant drugs and antianxiety drugs has been very extensive, and has already provided much relief.

The treatment of depression with monoamine oxidase inhibitor drugs and with the so called "tricyclic antidepressant" drugs has been an area of mutual interplay between academic labs and industrial labs. Academic scientists, seeking to understand the way in which these drugs work, have discovered important biological properties of certain types of nerve cells which allow these nerves to make and use their neurotransmitters. These two drug classes, monoamine oxidase inhibitors and tricyclic antidepressants, appear now to produce their major actions on nerve cells which use the neurotransmitters we call monoamines (more precisely, norepinephrine, dopamine and serotonin). In industrial labs, the process of chemical modification of the natural transmitters or the discovery of drugs which alter the conservation and metabolism of these monoamine transmitters has provided drugs with significant antidepressant actions. These drugs have also helped psychiatric distinguish between different categories of behavioral disease which can appear as depression. However, we need to know much more about the nature of the underlying biological

problems which occur in depressions, in order to understand their causes and to develop drugs which are better able to deal directly with the defective steps. The simple fact that biological concomitants of depression can be detected, that susceptibility to depression can be inherited, and that biological depression can be diagnosed directly by blood tests and by tests of the brain's electrical activity all attest to the conclusion I share with many other scientists, that there is a very real biological basis for depression, and that its causes, treatment and prevention demand that we clarify the pathology.

The state of anxiety and the drugs which are used to treat it are even further away from solution. Here we have drugs used "because they work" albeit with only partial success, to treat behavioral conditions assumed to arise from alterations in brain function. Anxiety is a symptom which many of us express under a variety of different conditions, real and imagined, and which can be manifest in any of several different sorts of behavioral problems from random motor activity to prolonged sleeplessness. Two classes of drugs used to treat these states, the barbiturates and the benzodiazepine tranquilizers, can be effective under physician control, but are subject to extreme abuse by patients frequently leading to fatal accidental overdosage, especially when combined with the overuse of alcoholic beverages. Drug development in this area of opportunity is based generally upon actions of drugs in animals or in test tubes which improves upon the effects of existing drugs with no real understanding of what it is these drugs do in humans to relieve anxiety. The possible neurotransmitter systems on which barbiturates and benzodiazepines may produce their anxiety

calming effects are only beginning to be understood. There is a faint possibility here that the brain may also surprise us once more by revealing that there are natural transmitter substances which have tranquilizing ability.

It is quite clear that as far as the biological bases of depression and anxiety are concerned (not to mention other important medical problem areas such as schizophrenia, alcoholism, sleep disturbances, obesity, and hypertension, all of which may be regarded as behavioral outcomes of misfunctioning brain circuts) much more research is needed.

It is perhaps gratifying for you to know that very active research does exist in this area, which has been supported almost exclusively by federal funds through the Department of HHS, especially through the Alcohol, Drug Abuse and Mental Health Administration. In fact, it is almost entirely due to the foresight of the National Institute of Mental Health in the establishment of the Psychopharmacology Service Center in the early 1960's that much of the fundamental research I have briefly mentioned was able to gain a foothold. Indeed, it is the area of psychopharmacological research in this very set of human problems areas which is being pursued by the cream of our researcher crop, in both academic labs and in the intramural labs of ADAMHA. Funding for this area has not at all kept up with the drain of inflation over the past decade. Despite the efforts of the previous administration and the recommendations of several prestigious panels (NIH Bio-Medical Research Panel, or Murphy Report; the Report of the President's Commission on Mental Health; the Report of the Califano Panel on Health Research Principles, and the recent

Institute of Medicine Panel on Opportunites for Research on Alcoholism) this area still remains sorely underfunded in funds for direct research and research training.

There are also critical shortages in the internal scientific staffs necessary to administer and coordinate this large research enterprise. Despite a modest increase in research budgets over the past 3 years, which have not yet returned the buying power of these research institutes to the pre-1968 levels, the staff sizes have been cut and are being cut further, leaving the operation of grant reviews and grants management critically understaffed. It is widely rumored that the Reduction-In-Force mechanism will be required to reduce the staff sizes in the current fiscal year, which will mean the unfortunate loss of able scientific administrative staff.

Given the Federal Government's almost exclusive role in the support of the fundamental and early drug development work, it seems illogical to me to stifle this important area where drugs are so vitally needed, both to prevent the use and abuse of legal and illicit substances and to alleviate more effectively the three conditions we have discussed: pain, depression, and anxiety.

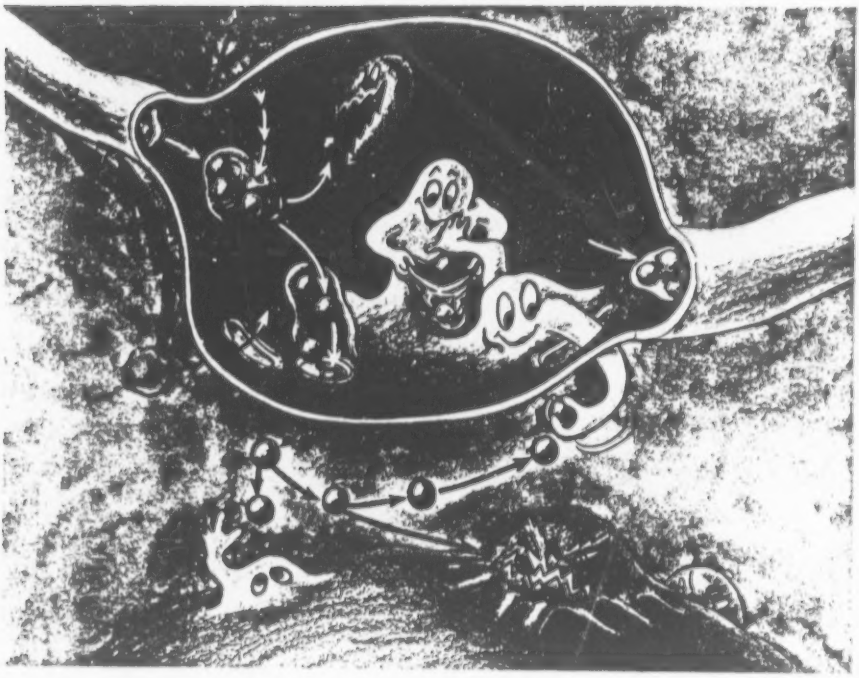
I would be very pleased to answer any questions you may have.

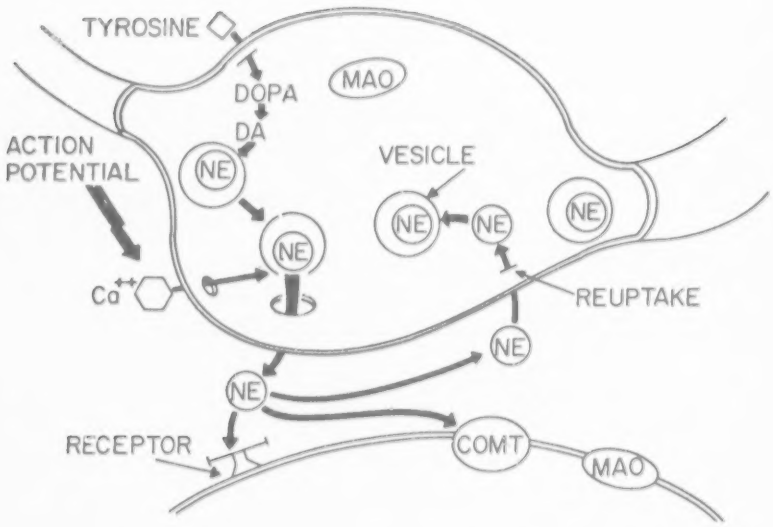
Congressional Testimony

Figure Legend

This is a schematic version of the different biological events which occur in the brain of man and animals at the points of transmission between nerve cells. Such transmission points are called synapses, and the chemical substance secreted by the pre-synaptic cell to transmit information to the post-synaptic cell is called a neurotransmitter. For the vast majority of synapses in the brain, the processs illustrated here is believed to be very close to what actually occurs. The neurotransmitter molecule is synthesized within the presynaptic terminal from dietary amino acids and stored in a small particle, called a synaptic vesicle. When the nerve fiber conducts an impulse to this transmission site, (lightening arrow indicating electrical activity) the mineral calcium flows into the pre-synaptic terminal and triggers the secretion of the transmitter into the synaptic cleft. Once released into the cleft, the transmitter molecules may react with post-synaptic receptors (outstretched hand) be metabolized by extracellular enzymes (at lower right) or be re-accumulated back into the nerve terminal for re-utilization. Using this general scheme shown in the illustration above, we can describe more specifically the events in a typical norepinephrine nerve terminal, shown at the bottom. Monoamine oxidase inhibitors prevent the metabolic breakdown of this transmitter, while tri-cyclic antidepressants prevent the re-accumulation of the transmitter after release. At points where anti-pain drugs work, similar events can be used to explain the major kinds of action: when natural anti-pain transmitters are released the post-synaptic cells do not

respond to painful stimuli. Alternatively, synthetic drugs which relieve pain act at the specific post-synaptic receptors where the endogenous anti-pain chemicals, such as the endorphins, are thought to act normally. It is not yet clear how anti-anxiety drugs may be analyzed in such terms since the sites where they act is unknown, and it is also unclear whether they act like endogenous factors or act to antagonize endogenous factors.

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Mr. SCHEUER. We do want to hear Dr. Goodwin. That was the way we started the procedure here. But since we're urging the FDA to have a flexible procedure, we will have a flexible procedure.

Let me ask you what you meant in that last sentence or two of yours when you urged flexibility. Were you referring to the FDA procedure for approving new drugs?

Dr. BLOOM. As I understand the procedures for approving new drugs, it requires testing with very large amounts of material, much beyond the levels at which they are intended to be used; particularly in early toxicity studies on rodents and other experimental animals, the amounts that are injected are extremely large.

When we're dealing with natural products that have natural effects in the body, it is to be expected that extremely large amounts in the body are going to do something that is quite different than what is going to be evolved when they are exhibited in that animal at the appropriate physiological dose. To insist upon toxicity not existing at any dose, to expect that no adverse effects will occur at amounts that are 10,000 to 100,000 times above what's necessary to be administered, I think that's inappropriate.

In the case of molecules that can be precisely mimmicking what man's own brain makes, I think that one must come up with a different set of standards for testing toxicity at levels of the drug that are relevant to the way in which it would be used in man.

Mr. GORE. Will the chairman yield on that point?

I have heard that criticism made quite frequently, of tests in which you give rats huges doses of one substance or another. I have also heard many scientists rebut that criticism by saying that it is an established scientific fact that large doses of a substance in animal populations are valid predictors of certain effects in human populations, and only by using large doses can one accelerate the timetable for discovering those effects.

And while what you say may be quite true for some kinds of toxicity, the criticism is inappropriate for discovery of carcinogenicity, teratogenicity, and mutagenicity.

Would you agree?

Dr. BLOOM. Yes, sir, but we're speaking about two separate issues. In the case where we're trying to devise a way to deliver to man larger doses of a hormone that his brain is already making, the issues of teratogenicity and carcinogenicity seem to me to be much more dubious side effects when the drug is a naturally produced compound.

It is certainly true that for particular drugs and particular species of animals, much larger amounts have to be given to a rat to produce an equivalent behavioral effect in man, and that would certainly also be true if we were making a synthetic analog or a drug that was contrived to be an antagonist, a blocking agent, from some natural hormone. Then all the questions that you raise may well apply. But I'm talking about naturally occurring materials that our brains make now and which have the ability to relieve pain. In those cases, I would think the rebuttal argument is not as appropriate as it might be in other cases.

Mr. GORE. OK. So you are not associating yourself with the common criticism of rat studies in that way; you're saying that in this particular instance the methodology should reflect the——

Dr. BLOOM. The spirit of flexibility I am trying to reach here is one that will target specifically on the breakthrough materials that are being discovered in the brain and are suitable starting points for the development of drugs.

Mr. GORE. Thank you.

Mr. SCHEUER. All right. We will suspend the question for just a few minutes, Dr. Bloom. Your testimony was most interesting, most thoughtful.

Do you want to ask any questions?

Mr. CARNEY. No, Mr. Chairman. I think we can listen to Dr. Goodwin and then we can question both panelists.

Mr. SCHEUER. Very good.

All right. We will be very happy to hear from you now, Dr. Goodwin.

Dr. GOODWIN. First, I will expand some of the points that Dr. Bloom made, and I did bring along a few pictures that might make these points a little easier to visualize from.

If you could put the first one up, please. The traditional direction in the development of drugs took a path in which more or less accidental and serendipitous observations were first made in patients, and then found their way into the research laboratory. Some examples in neuropharmacology are the drug lithium, tri-cyclic antidepressant, for the treatment of the major depression, and tranquilizers for use in schizophrenia. These drugs were all found by a kind of random process referred to in some of the earlier testimony.

Following these empirical observations a drug development process was used to try and sort out which of these random findings were really valid or which were not. Those findings that held up were then applied to patients as a relatively specific treatment.

In contrast, what has happened in the last 10 years—and this, I think, is a direct result of the tremendous explosion of new knowledge in neurobiology clearly one of the most exciting areas in biology today—as a result of that enormous explosion in knowledge increasing exponentially which is every year, we now have the possibility to think of drugs not based on accidental observations, but actually engineered or targeted drugs, that is, those developed from the basis of new knowledge of brain chemistry and brain anatomy.

To illustrate this approach come to mind: (1) Three examples the enkephalins, which as Dr. Bloom mentioned, are the synthetic efforts making an endorphin or a naturally occurring anti-pain substance, (2) a vasopressin analog, which I referred to in my written testimony, that appears to have potential for improving impaired human memory, and (3) new drugs related to the benzodiazepine receptor, commonly called the "valium receptor."

The next chart is an illustration of the complexity of the nerve cell in the brain. The point that we're interested in is the nerve ending, enlarged in the insert. The nerve ending is an enormously complicated piece of machinery, rapid developments in the last few years has enabled us to understand the function of these endings a great deal more—the next graph shows the synapse; in other

words, the connecting point between one nerve cell and another. It is across that synapse that one nerve, in effect, talks chemically to another nerve.

The main advance has been in identifying specific receptors, illustrated over there on the right. These are specific receptors which are chemically keyed or chemically designed to fit only into a specific transmitter or drug.

Research has shown that many synthetic drugs bind to a specific receptor site in the brain. This became a source of great curiosity to scientists, because we wondered why nature would have programed a specific protein in the brain for the benefit of a drug that was manufactured by Hoffmann-LaRoche? Hoffmann-LaRoche is a large company, but they don't have a direct tie-in to God. So why should there be a receptor in there for benzodiazepine?

This, of course, stimulated efforts by a number of investigators, including some in our own laboratories, to look for natural substances that might bind to that same receptor. So the receptor became a very quick, easy, and convenient way to screen for drugs which might have benzodiazepine activity. This would short circuit the enormous behavioral testing and the very expensive process of looking randomly through all of the possible organic molecules in the book to see which ones might have anxiety reducing or sedative properties.

If you can flip to the next chart.

I would like to mention a couple of examples of this process. My colleagues found that one of the compounds a naturally occurring one, that did bind to this receptor, is inosine, a purine. It was somewhat of a surprise to us, that inosine should bind to that receptor, but nevertheless, it did.

Based on this knowledge—a new compound, was synthesized. You can see its structure is partly different and partly the same as diazepam, which was the drug found earlier by the random process.

Laboratory studies showed that this CL drug appears to have pure anti-anxiety properties with little or no sedative properties in animals. Preliminary data from clinical trials, some in Germany and indicates that it has almost no sedative properties in humans. When you consider the problem that people receiving anxiolitics or valium-like drugs can have with driving when those drugs are combined with alcohol, its obvious why it is clinically helpful to have a drug which is not sedating and yet is a potent antianxiety drug.

Another example involves another receptor identified for adenosine, another purine, which occurs naturally in the body. Scientists synthesize a compound—EMD—with a chemical structure closely patterned after adenosine. Organic chemistry has advanced to the point where it's not too difficult, to synthesize a compound to order. It turns out that this EMD compound has, in fact, effects opposite to those of inosine. It's a very sedative drug and might be useful, for example, in the treatment of sleep disorders. So these were two examples in which a particular receptor binding encourages the search for an endogenous substance in a way similar to the endorphins which were found because of morphine's specific reception in the brain.

Flip over to the next one.

There is a new technique which has been developed in neuroscience called positron emission tomography, or PET scanning. PET scanning allows you to look at a radioactive substance as it is distributed throughout the brain. In this PET scan the different densities of radioactivity have different colors. In this particular scan the red areas are the hottest, the blue are the coolest. This way you can trace where a given chemical compound actually goes in the brain.

Within a couple of years this technique will be combined with receptor techniques so that radioactively labeled drugs can be traced to different areas of the human brain. This technique would help considerably in resolving the questions regarding relative side effects and beneficial effects of drugs since we know that some of the troublesome side effects of drugs relate to their localization in certain areas of the brain whereas the beneficial effects we can locate to areas of the brain that are responsible for the behavior we are trying to alter.

Using these techniques as a clinical screening device, we could obtain data that could never be obtained from animal studies. In fact, animal studies wouldn't be very relevant because species differences between experimental animals and humans are very great with respect to the brain. There is a certain limit to what we can learn from animal studies both with regard to safety and with regard to efficacy.

There is one other example I want to show you briefly which derives from more or less standard techniques now routinely available in major medical centers and which could become the basis for the design of new drugs.

Could you flip to the next chart, please?

As a routine in most research centers, one can obtain information about neurochemical substances, the neurotransmitters in the brain, and three of which I have just spoken of. We can also sample their end products called their metabolites, in the spinal fluid. This is a safe and really simple procedure if it's done by qualified people.

We were interested in the study of these metabolites, in major depression. This chart should help to illustrate how I am using the term depression in the context. On one end of the spectrum depression is a word we all use as a part of our everyday living experience; on the other end of the spectrum the word refers to an illness which results in about 75,000 suicides in this country each year. It incapacitates a segment of our society that prior to their getting depressed are often some of our most productive and effective citizens. Depression of clinical significance probably affects about one out of every seven Americans at some time in their life, and one out of every three families will have a member with clinically significant depression at some time.

Next one, Tom.

We were interested in a group of subjects who had made suicide attempts, since this is one of the major life-threatening consequences of depression; we found that one of the metabolites, that is one of the measures of these brain neurotransmitters, turned out to be very low in the patients who had made either successful suicides or particularly violent suicide attempts. You can see all of

those crosses and black-filled boxes are in the low end of the distribution of metabolites. Low concentrations of this metabolite seemed to be a marker, some kind of way of identifying suicidal potential in these patients.

The last board, shows a 1-year followup study of two different groups of people who had in common that they were admitted to the hospital because of a suicide attempt.

Among one group of people admitted to an intensive care unit after making a suicide attempt, 2 percent were dead after 1 year.

The second group were suicide attempters admitted to a psychiatric research ward after a suicide attempt, and had spinal fluid studies. Of those who showed a level below the median, or in the lower range, 22 percent of them were dead in 1 year. Thus the metabolite measure identified those subjects at the highest risk of later successful suicide.

To put this problem in terms of drug development, there are now drugs of the classic tricyclic type now being tested, which are specific for serotonin in the brain. In fact——

Mr. CARNEY. May I just interrupt for 1 minute for clarification?

Dr. GOODWIN. Yes.

Mr. CARNEY. When you say they're dead, do you mean they died of suicide?

Dr. GOODWIN. Yes.

It might well be possible in the not too distant future—using these techniques—to specifically select out patients who might be more responsive to a serotonin-active drug.

This kind of information will have to be incorporated into our thinking about the design of drug trials. If you had a large group of 200 patients in which you had no prior biochemical subtyping, you would have great difficulty showing that a new drug was any better than the standard drugs. One could use the argument that this was just another me-too drug.

It would be like saying if you had a drug for pneumococcal pneumonia and you tried to show it was effective or more effective than the ones available and you studied all pneumonias, including viral pneumonias and pneumonias due to other bacteria besides the pneumococcus, it would be very difficult to show that. Drug testing is going to have to start to incorportate some of these pretreatment biochemical measures.

I would like to end up with a comment in agreement with what Dr. Bloom said, and that is that it's very important to our drug development and drug testing process, both animal and clinical, that our scientific and administrative systems be kept up to date with the rapidly developing field of neurobiology. The changes in it have never been more rapid than we've seen in the last 5 years.

[The prepared statement of Dr. Goodwin follows:]

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Testimony of Frederick K. Goodwin, M.D.

Chief, Clinical Psychobiology Branch, NIMH

Before the House Committee on Science and Technology, Subcommittees on Natural Resources, Agricultural Research and Environment, and Investigations and Oversight

April 27, 1981

"Pharmaceutical Innovation: Promise and Problems"

"Breakthrough Drugs for the 80's"

The last 20 years has witnessed a virtual explosion in new knowledge concerning brain function, an area of science which has often been called "the last frontier." In parallel with these developments in neurobiology, clinical concepts of mental illness have been evolving towards an increasing recognition of the importance of biological factors. The old debates about psychosocial versus biological causes of mental illness occurred in the absence of hard data. Today such arguments are giving way to considerations of the relative contribution of psychosocial and biological factors to mental functioning.

The fundamental reason for the profound shift in our attitudes towards the mentally ill can be found in what is clearly one of the towering achievements of modern medical science - the development of effective drugs for the treatment of schizophrenia, depression, mania, and pathological anxiety. These drug treatments have resulted in substantial reductions in the need for hospitalization of the seriously mentally ill, the majority of whom can now function in the community. In addition, the advent of successful pharmacotherapy has brought psychiatry back into the mainstream of medicine, a

trend which has helped reduce the stigmatization associated with mental illness.

Until recently, the development of a new drug treatment in psychiatry would often originate from a somewhat accidental or casual observation in a clinical setting. Following this, investigators alert to the clinical literature would pursue this lead, applying systematic methods in order to sort out the observations that were valid. In this way a new drug would be discovered and this in turn would lead to the development and testing of other compounds in the same chemical family in the hope of finding drugs with similar but more specific therapeutic actions - and fewer side effects.

Today because of the rapid evolution of a fundamentally new understanding of the brain, it is becoming possible to start from observations of behavioral-biochemical relationships in the animal laboratory and move to the development of specific drugs for the treatment of mental illnesses. It is these recent developments which have focused interest on the process by which "breakthrough drugs" get from the lab to clinical trials.

I will briefly outline a few recent developments in the treatment of anxiety and depression to illustrate this new "fast-track" between the laboratory and the patient.

Very recently, a series of studies in animals lead to the discovery of a specific "receptor site" for benzodiazepines (valium-like drugs) in the brain. What was uncovered was a chemically specific site on brain membranes onto which valium-like drugs would bind and through which they exert their pharmacological action; these benzodiazepam binding sites were found to have a characteristic distribution in the brain. Reasoning that nature had not programmed a specific brain site for a compound not naturally found in the body (i.e., the drug)

investigators in my laboratory began a search for a naturally occurring substance in the brain which would also have the property of binding to this receptor. They discovered that a class of compounds called purines, previously unsuspected as transmitters of messages between nerve cells, did bind to the "valium receptor" and in fact did act like valium in various behavioral tests. Working from the fundamental chemical structure of these purines, pharmaceutical companies have now undertaken the development of new drugs and have tested them for anti-anxiety properties. One such drug has now been shown to have very potent anti-anxiety effects with little or no sedative effects. If this drug were to become available clinically it would represent a major advance since one of the problems with anti-anxiety drugs is their tendency to cause sedation.

Another example of a new drug developed directly from laboratory studies rather than from any accidental clinical observations is vasopressin, a peptide that was found in areas of the brain known to be important in memory and cognitive function. This discovery led to animal tests of vasopressin's effects on memory and it was found to substantially enhance memory. Following up on these animal studies NIMH investigators administered a vasopressin-like compound (DDAVP) to severely depressed patients who were suffering from the memory deficit common to this illness. All of the patients showed substantial enhancement of memory and cognitive functions and some of them had a full antidepressant response. Further work is necessary to develop a vasopressin-like drug which does not have effects on blood pressure.

Combining the new technologies of positron emission tomography (PET scanning, which can trace radioactively labelled substances to specific brain areas) with specific receptor binding for drugs, will allow us to examine precisely where in the brain a drug is acting. With these techniques it will be possible to screen for compounds which are taken up by the brain selectively in those areas where they are needed for a particular clinical effect without going to other areas where they could produce unwanted side effects.

Development of new drugs for the treatment of serious depressive illness has recently been influenced by discoveries of biochemically different types of depression. The uncovering of these subtypes of depression has been possible because of the availability of sophisticated techniques developed by clinical researchers to test biological hypotheses of mental illness. These techniques include the measurement of important brain chemicals and hormones in spinal fluid and blood, sophisticated electroencephalogram (brain wave) techniques which measure the brain's response to sensory stimulation (evoked response) and the positive emission tomography (PET) scan which allows for the study of metabolism in specific areas of the brain in a living patient. Using an array of these techniques investigators have noted biochemical heterogeneity among groups of depressed patients and have explored the relationship between different biochemical subgroups and clinical phenomenon. Today, new antidepressants are being developed that would more specifically target the particular biochemical abnormality identified in different subgroups of patients.

Another important clinical phenomenon which is being studied in relation to biochemical differences is suicide, one of the leading causes of death of Americans under 60. At the NIMH we have been studying spinal fluid levels of the metabolite of serotonin, one of the important neurotransmitter substances in those areas of the brain regulating mood and mood-related behavior. We found that people with life histories characterized by high levels of aggressive and impulsive behavior had relatively low levels of serotonin. Studying depressed patients we found that those who made suicide attempts had serotonin levels in the very low range. Thus, the combination of being depressed and having an inate tendency toward aggression and impulsitivity would seem to make an individual more vulnerable to suicide. With this measure it is now possible

to predict suicidal behavior in advance. Related to these studies we have been evaluating a new antidepressant drug which specifically enhances brain serotonin function as a treatment for suicidal depression. Suicide is the cause of at least 75,000 deaths a year in this country alone.

It is important to emphasize that our capacity to move forward in the development of new and more specific drugs for the treatment of psychiatric illness depends on the continued parallel development of both basic research techniques and high quality clinical research. The best biochemical techniques in history would be useless without carefully studied, well defined patient groups in which to apply them. For example, we must improve our techniques for defining and quantifying various subtypes of major depression, the relationships between these subtypes and the response to different medications. We also must continue our investigations on the interaction between drug response in psychiatric illness and psychosocial factors. Modern treatment techniques involve the combination of psychopharmacology and psychosocial techniques.

We need continued laboratory research in order to develop meaningful animal models for depression and anxiety in order to allow for the rapid testing and screeing of drugs with antidepressant or anti-anxiety potential. At the same time we must realize that the complex clinical conditions of depression or anxiety probably have characteristics which are uniquely human and therefore not completely analogous to animal models. Because of this it will be necessary to continue and strengthen clinical research in parallel with basic laboratory research.

Finally, we must remember that the vitality of both clinical and basic research depends upon the availability of easily accessible bridges between the laboratory and the patient. The new generation of drugs is the most important bridge we have and we must all work to keep the traffic flowing. Although

much progress has been made, mental illness still takes a terrible toll and much remains to be done. Modern neurobiology and pharmacology offer an unprecedented opportunity and we must be prepared to take it.

Mr. GORE. Dr. Bloom, you say in your testimony that research into the biological basis of depression and anxiety is supported almost exclusively by Federal funds. Why are the pharmaceutical companies spending little money in this area? Is that a fair implication from your statement, and if so, what is the reason for it?

Dr. BLOOM. The drug companies are primarily interested in developing drugs to be used in clinical trials, but the research to which I refer is the basic kind of research that Dr. Goodwin just summarized, which is to work on the mechanisms of the disease and the way in which drug molecules might be effective in treating the disease. Once those basic properties of the synapses are known—that funny little cartoon I put at the back of my statement shows some ways of looking at how drugs act—then they can be used by pharmaceutical laboratories to develop new drug molecules which can then be brought to clinical testing. So there is a very real interplay between us, but we concentrate on different parts of the puzzle.

Mr. GORE. Dr. Goodwin?

Dr. GOODWIN. I might add that there is a sort of hidden drug company contribution to the basic research that is supported by the Government, in providing many of the experimental drugs that we study. That is, what they are geared to and have enormous capacities for manufacturing drugs and employ large numbers of organic chemists. The NIH, for example, has never attempted to set up its own mechanism for the manufacture and testing of drugs which I think is wise. Since the drug companies have this machinery in place, many of the drugs used by us in experimental animal tests are provided by the drug companies, and often there is no commercial payoff.

Dr. BLOOM. But it helps us to understand better the mechanisms that the brain uses to express these complicated behaviors and how to analyze them, so there is a very effective combination effort going on.

Mr. GORE. In the industry as a whole, the ratio of basic research to sales in deflated dollars, after you adjust for inflation, has decreased in the last two decades. Is that trend also true for neuropsychopharmacology?

Dr. BLOOM. In terms of the drug companies' investment in it?

Mr. GORE. Yes.

Dr. BLOOM. Well, it depends, I think, on the particular corporation. Some corporations have taken up the challenge of the breakthroughs in the brain and utilized them. Others have decided that it's too complicated and without a significant critical mass they can't afford to compete effectively and so they've gone by the wayside.

Mr. GORE. But you wouldn't have figures for the industry as a whole?

Dr. BLOOM. No, sir, I'm afraid I don't.

Mr. GORE. That's understandable.

Dr. Goodwin, would you know the answer to that question?

Dr. GOODWIN. No, I don't have that data.

Mr. GORE. You referred in your statement to the fact that many scientists call the brain the last frontier. Do you mean that many

of the pharmaceutical breakthroughs in the future are likely to be in this particular area?

Dr. GOODWIN. Well, I think the brain presents, in contrast to any other organ, special excitements, challenges, and ethical problems. I mean, you can talk about breakthroughs for treatment of mental illness; you can also talk about mind control. Questions arise whether drugs should be used to enhance normal function, and the question of what is normal, and should someone who has, for example, no memory defect take a drug which enhances memory, and is this really an enhancement?

This is also true of drugs that might enhance creativity now being tested. These are all issues which I think should not be left up to physicians or pharmacologists alone. They involve some very difficult ethical questions.

Mr. GORE. I might say for the record that the Investigations and Oversight Subcommittee has a series of hearings underway in this area of bioethics. One of the things we intend to look at is vasopressin.

Are you aware of the use of vasopressin today for memory enhancement?

Dr. BLOOM. Actually, Dr. Goodwin's lab has done studies on exactly that.

Mr. GORE. Outside of the laboratory?

Dr. BLOOM. In human beings?

Mr. GORE. Yes.

Dr. BLOOM. Yes. It is also marketed for that purpose in Great Britain.

Dr. GOODWIN. Yes, it has been used—we have done clinical research with it, as I mentioned in my statement, and there are a number of European studies. Our studies have been in depressed patients and also some normal controls. The European studies have been in people between the age of 50 and 70 who often begin to have a normal deterioration in certain aspects of memory.

Mr. GORE. And what have the results been?

Dr. GOODWIN. They have been very enccuraging so far, particularly in the depressed patient. It seems to be most effective where there is already some problem, but only in those patients who have deficits that are not based on structural loss—in other words, it doesn't help too much in somebody who has senile dementia due to degeneration of nerve tissue. It produces a small enhancement, but in terms of the magnitude of their problem, it doesn't help that much the enhancement of normal memory seems to be relatively modest. But in normal people who seem to have some slippage of memory due to the process of aging,—the European data indicates that they rather improve substantially.

The problem with vasopressin at the moment is that the only marketed form of the drug also affects blood pressure and body fluid retention. In fact, that's what it's sold for, for the treatment of diabetes insipidus, which is a form of excess urine formation. It is probably too complicated to use outside of an experimental setting until somebody is able to make a molecule that has only the memory effects and not the other effects. That has been done in the laboratory; it has not yet been done in humans.

Mr. GORE. You mentioned the antidepressant for the treatment of suicidal depression by enhancing the brain serotonin.

How are those studies progressing?

Dr. GOODWIN. They are progressing in several centers throughout the world, including our own research wards at NIH. It has now been possible to identify in humans these drugs do have selective effects on serotonin. They are clinically effective antidepressants, but the long-term followup of whether the patients on these drugs would, in fact, have a lower suicide rate is still unknown.

Mr. GORE. Dr. Bloom, is it fair to say that research on antianxiety drugs still utilizes for the most part the so-called hit or miss approach rather than the new sophisticated molecular model approach?

Dr. BLOOM. I think you have seen in Dr. Goodwin's slides here that in the recent activity on new tranquilizer development it is possible to use molecular techniques to probe at it. What is not yet quite clear in the molecular technique, is whether there are not additional ways to produce a good tranquilizer that doesn't depend on the binding of the original molecule, the benzodiazepines. These recepter-binding techniques are good for predicting structural developments in drugs that will act at that site, but we have discovered time and time again the brain has many ways of achieving different functional properties, and as we talked about pain development, there are drugs other than natural morphines that can also cause diminished responsiveness to pain, and many of those may also be better routes to the development of good antianxiety compounds.

But I would say until recently that has not been the case in anxiety research.

Mr. GORE. In answering those questions, you talked about endorphin, the body's own pain killer, so to speak. You said that clinical tests are being conducted in Japan, but are more or less impossible to do in the United States because of our regulatory rules.

What rules are you referring to?

Dr. BLOOM. Those would be for the development of IND's and protocols for the treatment of cancer patients for pain and for the treatment of childbirth pain. These are very difficult areas apparently to establish clinical studies in the United States. Only one IND has been issued for the study of endorphin, and that has been tabled for about 2 years now while the FDA is requiring data and analyzing a few of the early case reports that were done. The peptides were used in that case to treat something else—they were used as a possible way of relieving drug addiction or of treating mental illnesses like schizophrenia or depression.

The use for them in the key area of providing long-lasting pain relief in a way that exposes only limited parts of the nervous system to the endorphin, that probably won't be possible to do in the United States, I don't think, for several years.

Mr. GORE. All right. That's all the questions I have.

Thank you, Mr. Chairman.

Mr. SCHEUER. Well, would you elaborate on that? You said it won't be possible in the United States. Why is that?

Dr. BLOOM. Theoretically it's possible to do them.

Mr. SCHEUER. You have a statement there that says straight on, on page 4, that such clinical research experiments are more or less impossible to do in the United States because of our regulatory rules.

Dr. BLOOM. Because at the moment we don't have approval, based on the fact that toxicity studies are not available to achieve the level of approval that would be required to start to do clinical research in the United States.

Mr. SCHEUER. To achieve a level of approval?

Dr. BLOOM. That's right. To be able to do the phase I studies, a large amount of toxicity study has to be done. The amounts of the peptide that are required to do those toxicity studies are enormous. The synthesis of 1 milligram of endorphin costs perhaps $1,000, so to acquire the large numbers of—the hundreds of milligrams that would be required to do toxicity studies, at levels that are really a millionfold off from what would be necessary to treat the patient, it will be a very expensive thing. And since the endorphin molecule itself is not the proprietary product of the pharmaceutical industry, it would be required for a research laboratory to promote these studies. At the moment, that's not possible to do.

Mr. SCHEUER. Would you say that—I don't know if you were here before——

Dr. BLOOM. Yes, sir.

Mr. SCHEUER. But I asked one of the witnesses whether the development of these new molecular, or the development of drugs that you design in the laboratory is through fiddling with molecules.

Has that simply been an incremental add-on to the problems of the FDA, or is this sort of a critical mass or a quantum jump into a whole new area of research that they're not equipped to deal with?

It seems to me that what you have just said indicates that they are totally out of synch with the realities of the new drugs that they're going to have to cope with and approve, and that the present system has become dysfunctional. Would that be a fair statement?

Dr. BLOOM. The system as it exists has been slow, but I suppose fair, in dealing with the kinds of compounds that were being developed before. But given the available new knowledge that we have, and what we can very confidentally predict will be occurring within the next months to years, the current system will be totally incapable of applying the old rules to the new kinds of treatments.

Mr. SCHEUER. Well, it's totally incapable now.

If you say they can do research in Japan that we absolutely can't do here——

Dr. BLOOM. Clinical research is allowed to be done there. The peptides actually are made in the United States and sent to Japan to be studied.

Mr. SCHEUER. What do you think ought to be done? I mean, if you were sitting right here, what role do you think Congress has in remediating that situation?

Dr. BLOOM. Well, sir, it seems to me that it ought to be possible to encourage the FDA to speak with the scientists who are doing the research and to try to equip themselves to understand the nature of the molecules that they're dealing with, and the dose

ranges, and how they differ from the old kinds of medications that have been available.

Mr. SCHEUER. Dr. Goodwin, you're familiar with everything that Dr. Bloom is saying, and you're Government civil service. What do you think the remedy ought to be to——

Dr. GOODWIN. That's why it's more difficult for me to answer that question. [Laughter.]

Mr. SCHEUER. Sure. Well, we're sort of putting you on the spot and asking you to bite the bullet.

Dr. GOODWIN. First of all, I'm not sure, in response to one of the questions earlier, about how much of the current situation is built into the law and how much is the way in which the FDA conducts affairs.

Mr. SCHEUER. Give us your thoughts on that, because if the remedy is here in Congress, and if we're part of the problem, we want to know that. We would like your recommendations on where the law should be changed.

Dr. GOODWIN. Well, I should say I can't speak for the FDA and I am only speaking as an individual scientist.

Mr. SCHEUER. I understand that.

Dr. GOODWIN. But I do have some appreciation from friends of mine in the FDA, that at least some individuals at the operational level would appreciate a little more flexibility—and I think somebody brought up this issue about responsibility. They are always the brunt of every sort of concern about a negative effect of a drug, and they end up being caught, from both sides, both from groups that might represent or speak for consumers who are worried about protecting people from drug safety problems, and then they are under the gun sometimes I think from people who feel that things ought to be speeded up. So they're in a very difficult position.

My own feeling is that we have to preserve our capacity to be surprised; that is, the system has to have enough flexibility in it that the unexpected can be dealt with, because that's what science is all about.

Mr. SCHEUER. But he's just told us that the unexpected can't happen because we can't do the work in the lab that might produce the unexpected.

Dr. GOODWIN. Well, he was dealing with a specific example of a drug which is enormously expensive, that is, a natural substance. Now, in this case——

Mr. SCHEUER. Well, it's not actually enormously expensive at the levels of treatment that could be predictable.

Dr. GOODWIN. That's right.

Mr. SCHEUER. It's only enormously expensive when you have to add a multiplier of 100,000 and require this incredible multiplier, as Congressman Gore explained it a few minutes ago, in order to contract the timeframe.

Dr. GOODWIN. I am sympathetic with some of the people in the FDA who feel that they would like the flexibility to take a look at drugs which are natural substances and not require all of the animal testing that is required for an organic molecule.

This is true, also, because of the fact that you can be misled in the wrong direction. That is, as I said before, the brain is the organ

most specialized in humans, and so an animal finding isn't ultimately going to be as helpful as a clinical finding. In some cases, the very information that is needed about safety has already been obtained from patients studied in another country. In that case, it would seem that the formal requirement of two species being tested for 30 days could be waived to the Commissioner or the Director of the Bureau of Medicine or somebody who would have the legal right to say, "we already have the human data."

Mr. SCHEUER. The data that has been developed in Japan?

Dr. GOODWIN. Right.

By the way, I might say, there is now a network of international cooperation among investigators in which it is fairly easy to identify centers of excellence around the world that are quite comparable to our best research centers here.

Mr. SCHEUER. The degree to which the FDA recognizes foreign medical data would not reflect that statement.

Dr. GOODWIN. I'm not sure of the history of that. I think that it's relatively recent development that the European centers have come up to American standards in the last few years. There was an earlier period when it probably made some sense to be more cautious about data from other countries.

Mr. SCHEUER. Congressman Carney.

Mr. CARNEY. Thank you, Mr. Chairman.

I would just like, for my own clarification, to get a historical perspective on neuropsychopharmacology. That is one of the newer branches of pharmacology, if I'm not mistaken; is that correct?

Dr. GOODWIN. Yes.

Mr. CARNEY. Was it about 1940 when we first started working in that business?

Dr. GOODWIN. Really 1950.

Mr. CARNEY. When we did get in that business, was it heavier on the industry side than, say, on the government side? For instance, was it the government who discovered compazine or thorazine, or was it Smith, Kline & French who discovered that type of medication?

Dr. GOODWIN. The original tranquilizer was discovered by an investigator working in a European drug company, but it was based on a clinical observation in a university clinic in which the drug company and the university clinic had a close working relationship. Thus the drug company and the university shared the discovery.

Mr. CARNEY. So prior to the 1950's, there was great discussion on how to handle this problem, whether you could do it through pharmacology or not, and not a whole bunch of attention was spent on it, either in the universities, in private enterprise, or supported by government; is that correct?

Dr. GOODWIN. That's correct.

Mr. CARNEY. And then finally we made these—I guess, through serendipity, we made some breakthroughs, or a combination of both, which we discussed, in the first half of a new field, and then if the charts make sense to me, as I think they do, we discovered something new, even further complicated, much more expensive to get to, and that is the body's own chemicals in a neurological system, if I'm using the right terms, which are very, very expensive

to produce, and have different parameters, in your view, to deal with as far as toxicity and everything else concerned.

Am I putting this together in a way that you would agree?

Dr. GOODWIN. Yes, I would agree that these new parameters mean we need more flexibility for implementation. Some of the parameters are expensive, others are difficult to get at. None are universal.

Mr. CARNEY. But as a natural substance that for some reason our body has become unable to produce, or perhaps overproduces, there should be different parameters to deal with that as far as toxicity and that type of thing, when you're dealing with a biochemical agent, a blocking agent, that has other effects on the body, contradictory effects on the body; is that what you're trying to say?

Dr. GOODWIN. Yes; a foreign substance should be thought of as a foreign substance; a natural substance should be thought of as natural.

There is one exception, however, or one caution. A natural substance is made in one part of the brain and it generally stays where it's made and it does its work where it's made. When we give these as drugs, we are giving them to the entire body, as it were, and some of them we can track and say they are selectively or relatively selectively going only to one place. So I would say that a synthesized natural substance is somewhere between a drug and a true natural substance. That is, a true natural substance is confined to the area of the brain where it ought to be. A drug which is based on a natural substance is not as foreign as a foreign substance, but it is still——

Mr. CARNEY. Introduced to the body but not necessarily going to the one part of the body where it traditionally has housed itself, and only housed itself there?

Dr. GOODWIN. That's correct.

Mr. CARNEY. We do have drugs, however, that will do that or go to that particular function or that type of tissue?

Dr. GOODWIN. Right.

Mr. CARNEY. In nuclear medicine we can pinpoint a drug that will be attached to A, whatever, and we know where it's going to go and we can follow that.

Would that hold true in some of the pharmacology that we're dealing with in neuropsychopharmacology?

Dr. GOODWIN. Yes; and as I said, using techniques from nuclear medicine, like the PET scanner, we can, in the not too distant future, actually trace in a living subject, without any problem, where those drugs are going.

Mr. CARNEY. OK. We have then had participation from the private sector to an extent when we were dealing with the first level of this new frontier.

Now, on the second level, there seems to be some sort of resistance, probably because of the complexities of it and the problems with doing the R. & D., the clinical research, because of parameters that are set up by Federal agencies, et cetera; is that correct?

Dr. GOODWIN. Well, I think it depends, as Dr. Bloom said, on the drug. There are some drugs that the drug companies have been very eager to develop analogs to, like vasopressin. They're working very hard on that. All the work on that is, in fact, pharmaceutical

company work, because it involves complex organic chemists and they have the talent to do that.

Mr. CARNEY. And if I may make one concluding statement, I would think I would not be far from wrong by complimenting everyone involved in neuropsychopharmacology for the job that they have done from 1950 to 1981. I mean, in that 31-year timeframe we have made breakthroughs where we have practically emptied out our hospitals around the Nation. In some instances, where previously where we could only put people in a hospital and leave them there, we have managed to empty out many of those facilities. We have a long way to go, but it's not as bleak as we might think it is. We have made major breakthroughs, and with the help of Government, both from the financial side and from the reduction of some of the parameters and requirements of the FDA and other agencies, and the research laboratories, and by swinging that research into the clinical application, we can expect to have even greater breakthroughs; is that correct?

Dr. GOODWIN. Absolutely, unquestionably.

Mr. CARNEY. I think we've got a job to do, Mr. Chairman.

Thank you very much.

Mr. GORE. Mr. Chairman, if I might make a request, I think it might make sense for us to ask the FDA to respond, for the record, to the proposal that test protocols for substances naturally occurring in the human body be modified so as to permit approval for this stage, the clinical study stage that we're discussing, without the normal massive doses that are used for determining toxicity when other substances are involved.

If, in fact, we can make a legitimate distinction between these two categories of substances—those naturally occurring in the body and other kinds—then it might make a lot of sense for them to modify their test protocols. But I would like to hear their response to that specific proposal for the record. If it can be done, we might make some real progress here.

Also, I would like to request that for the record we ask the response of the Justice Department, which normally defends the United States in lawsuits, to the proposal we heard on sharing the legal liability for vaccines, where the work is done properly and it is administered properly.

If we get responses from the Government on those two panels, maybe we can come up with some fine tuning and some specific solutions for these broad categories of breakthrough drugs for the eighties that this hearing has focused on.

In the other areas, perhaps the prioritization—a word that is unpopular but has found its niche in our language, nonetheless—to speed up the approval process in other areas where there are not generic improvements in the protocols.

Mr. SCHEUER. So ordered. We will do that.

On the matter of working with the Justice Department, perhaps we might want to cooperate with the Health and Environment Subcommittee because that falls squarely in their lap. I was on that subcommittee several years ago when they had this whole problem, and they considered it extensively.

Mr. GORE. While I'm talking about the record, Mr. Chairman, just briefly, I would like unanimous consent to put in the record,

following the testimony of Dr. McMahon, the clarification on the subject of informed consent's effect on liability exculpation. We had an exchange on that, and I am informed by staff that there is a regulation pending on that very subject right now. I would like unanimous consent to put a summary of that relationship in the record.

Mr. SCHEUER. So ordered.

Well, we have imposed on your time and your patience and we appreciate your testimony very much. It was obvious how interested and involved we were in what you had to tell us. Thank you so much.

We will now go on to the witness on cardiac drugs, Dr. Elliot Antman of the Harvard Medical School.

We're running late, Dr. Antman, so why don't we plan on chatting with you, listening to you and chatting with you for about 20 or 25 minutes, and then we'll devote the last half hour to the two witnesses who will testify on prostaglandins. So if you would take 7 or 8 minutes and sum up your testimony, and then I am sure we will have questions for you, if the history of this afternoon's hearings is any evidence thereto.

STATEMENT OF DR. ELLIOTT ANTMAN, HARVARD UNIVERSITY SCHOOL OF MEDICINE

Dr. ANTMAN. Thank you.

Let me first introduce myself. I am a cardiologist and I have an academic appointment at Harvard Medical School. My clinical responsibilities are at the Brigham and Women's Hospital in Boston, where I direct the coronary care unit.

I would like to discuss with you today very briefly some of the new cardiovascular agents which either have recently become available or are under clinical investigation.

Do you have a copy of my outline?

Mr. SCHEUER. Oh, yes.

Dr. ANTMAN. I will provide you with a full written testimony in the timeframe that you have asked us to provide it in.

Mr. SCHEUER. If the witness will yield, normally we're very strict and stern, and sometimes even slightly unpleasant, to people who don't get in their testimony well in advance. But in this case we want to thank you for having substituted for a witness who couldn't make it and for having put this together very much at the last minute. We are very grateful to you for that.

Dr. ANTMAN. Under the first section I have summarized six categories of new cardiovascular agents; I will highlight only a few of them.

New cardiovascular drugs include compounds known as calcium channel blocking agents, which are useful for a number of cardiovascular conditions; antiarrhythmic agents; beta adrenergic blocking agents; antihypertensive agents; a group of agents known as inotropic agents, which are cardiac stimulants; and finally, diuretics, which increase urine flow.

One might add to that list the compound intravenous nitroglycerin, which is an intravenous preparation of a commonly used drug, nitroglycerin; ordinarily taken sublingually—below the

tongue—in a tablet form. Intravenous nitroglycerin is still investigational but it is a promising new agent being used widely.

I want to particularly emphasize the calcium channel blocking agents since they have been alluded to earlier today, and I think we're going to be hearing a lot more about them in the future. The reason that we will be hearing so much more about them is that they are efficacious for a number of cardiovascular conditions.

It is always striking when we find a drug which is helpful for a particular condition, but it is especially striking when we have a single class of agents which is active against many cardiovascular disorders. Let me tell you exactly what I mean by that.

First, the calcium channel blocking agents, as the name implies, inhibit the movement of calcium ions across various cells in the body. With particular reference to the heart, they inhibit the movement of calcium into cells which control the natural pacemaker and speed of the heart; that is, the heartbeat. The calcium blockers are also involved in controlling the force of cardiac contraction, and in addition, are involved in controlling the tone of blood vessels throughout the body—arteries generally throughout the body, and in particular the arteries which provide blood supply to the heart muscle directly, the coronary arteries.

There are a number of agents which fall into that category. We might as well be familiar with some of the names. They include drugs such as nifedipine, verapamil, dilfiazem, peshixilene, lidoflazine, and prenylamine. I'll give you a full list of that in my written testimony.

Now, I have brought an example today of nifedipine, and I think it serves as a useful example of some of the things that Dr. McMahon had alluded to in his testimony. Let me just tell you the history of this compound because I think it's very interesting.

It was synthesized by chemists in Germany in 1967. It was introduced for clinical investigation in Germany in 1970, and by 1975 it was approved as a general prescription item in Germany. It was brought to the United States shortly after that, but it has not yet been approved in the United States.

Between 1975 and 1980, in addition to Germany recognizing it as a general prescription item, 46 other countries have approved it as a general prescription item. I will give you representative examples.

For example, in 1976, Spain, Mexico, Brazil, and Japan approved nifedipine and in 1977, England, 1978, Poland and Rumania, 1979, France and Israel, and finally in 1980, Sweden. These are listings which I checked with the drug company this morning before I left Boston.

This particular compound is helpful against a number of conditions, in particular angina pectoris, which is a pain in the chest due to poor blood supply to the heart muscle.

Like nifedipine, there is another compound of the calcium channel blocking group called verapamil, which is particularly helpful for abnormal heart rhythm, in particular supraventricular tachycardia, which is a very rapid rhythm originating in the top portion of the heart.

This whole group of compounds is also helpful in patients with hypertension, and finally, a condition known generally as cardio-

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myopathy, which is an intrinsic abnormality of the heart muscle. The abnorminality I'm referring to here is one known as hypertrophic cardiomyopathy, where essentially there is an excess amount of muscle which causes a number of derangements of heart function.

Now, the second group of agents are the antiarrhythmic agents which are particularly important for stabilizing heart rhythm, and I would like to highlight to you a population of patients who are in urgent need of antiarrhythmic agents, especially some of the investigational agents in the United States.

There is a population of patients who suffer sudden cardiac death. They number between 400,000 and 500,000 a year. By sudden cardiac death, I mean a death which is a natural process but unanticipated; in other words, the patient was in a previous state of health common to that patient, and then sudden death occurred. It's a matter of how long you want to define how long it took the patient to actually expire, but usually a definition of about 24 hours is used. In the vast majority of cases death is due to ventricular fibrillation, which is an ineffectual contractile pattern of the heart.

To prevent that from occurring, there are a number of drugs which can be used, which are being investigated in the United States today. There's a long list of them. We have a number of techniques for assessing these drugs, and they include exercising the patient and watching the response of the heart rhythm to exercise, monitoring the heart using an electrocardiogram on a long-term basis, or performing sophisticated elctrophysiologic stimulation.

In addition to the antiarrhythmics, there is a broad class of beta adrenergic blocking agents. There are a number of them which are under investigation and they provide a number of different advantages over the ones which are presently available in the United States.

One might ask the question, why should we have so many agents available if we have three beta blockers in the United States right now. The major advantages to having additional agents is that they have differences in the dosing requirements, they have differences in the side effects, and there are relative differences in their efficacy for certain cardiac conditions.

I would like, in the interest of time, to just briefly summarize the implications of this ever-expanding group of cardiovascular drugs. I see three important points. First is education, education of everybody: the patients who need to know about these drugs, especially the possible adverse effects which they might have, and the physicans who are going to write prescriptions for these new drugs.

I am not so concerned about physicans who are in the academic sphere because they are likely to have the opportunity to attend national meetings or are actively involved in investigation and are more likely to be up on the literature. It is the physicians out in the community who are going to be dealing with these new drugs that I think need to be educated. I think we might look for a role of the Federal Government in providing the sources for that type of educational process.

Another important point is the concept of drug interaction. As we increase the number of drugs available to the practicing physican, we also increase the number of potential interactions which he must be aware of. In order to simplify that process, I think it would be useful if there were some central repository of information regarding known drug interactions or new drug interactions as they were discovered. One conceivable place would be, for example, the National Library of Medicine and the computer system which is available. One could regionalize computer hookups in various parts of the country so that important information would be available.

The final implication of this enlarging list of drugs relates to the regulatory process which we have discussed before. I would like to join in the discussion about the use of foreign data since I think nifedpine is an excellent example of a drug where there are a significant amount of data available in a large number of countries and in several million patients. I think we should utilize those data more effectively, not only in this type of drug, but in all drugs as they are put forth in clinical investigation.

One difficulty that often arises relates to a number of small centers investigating limited numbers of patients in various parts of the United States. If we were to have some cooperative effort, I think we could gather data a lot more effeciently and effectively. One study which actually is already being funded by the NIH involves agents which are useful in reducing the size of a heart attack. This is a multicenter study known as the Milis study, which is funded by the Federal Government.

I think, most importantly, we should simplify the methods of data collection and vastly reduce the number of forms which need to be filled out. I haven't brought the forms that would need to be filled out to treat a single patient with nifedpine, because they're very extensive.

Thank you very much.

[The prepared statement of Dr. Antman follows:]

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April 30, 1981

Mr. Jonah Shacknai
821 House Office Annex #2
Washington, D.C. 20515

Dear Mr. Shacknai:

Enclosed please find a copy of the formal written testimony relating to the Joint Hearing of the Subcommittees on Natural Resources, Agricultural Research and Environment, and Investigations and Oversight which occurred on April 27, 1981. In this written testimony, I have attempted to briefly review important new cardiovascular agents and discuss some of the problems with the current regulatory process. I have provided some additional source material in appendix form which I hope is useful to you. If you require any additional information, please do not hesitate to contact me.

Thank you very much for giving us the opportunity to participate in this important endeavor. Please extend my best wishes to Representative Scheuer I am sure that our paths will cross again and I look forward to spending more time with you.

Thank you very much.

Sincerely,

Elliott Antman MD

Elliott M. Antman, M.D.

EMA/djk

TESTIMONY OF

ELLIOTT M. ANTMAN, M.D.

ASSISTANT PROFESSOR OF MEDICINE

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before the

House Committee on Science and Technology

Subcommittees on Natural Resources, Agricultural Research and Environment,

and Investigations and Oversight

House of Representatives

Monday, April 27, 1981

PHARMACEUTICAL INNOVATION: PROMISES AND PROBLEMS

There are a large number of new cardiovascular agents which have recently become available in this country or are currently under clinical investigation. These include the calcium channel blocking agents (Table 1), antiarrhythmic agents (Table 2), beta adrenergic blocking agents (Table 3), antihypertensive agents, inotropic agents (cardiac simulants, Table 4), diuretics(Table 5). In addition, mention should be made of the investigational agent, intravenous nitroglycerin. This is a promising new parenteral preparation of a standard cardiovascular medicine, sublingual nitroglycerin. Important aspects of several of these new classes of agents will be discussed briefly.

Calcium Channel Blocking Agents

The calcium channel blocking agents are useful in the treatment of a number of important cardiovascular disorders. These drugs act by inhibiting the movement of calcium ions across cell membranes in the heart and blood vessel walls. The inhibition of calcium ion movements in electrically excitable cells has important effects on the conduction of electrical impulses within heart tissue. By controlling the movement of calcium ions into the smooth muscle cells of the walls of arteries throughout the body, abnormal vascular tone and "spasm" can be corrected. This is particularly important in cases of spasm of the coronary arteries, which are the major arteries supplying blood to the heart muscle.

The numerous clinical uses of the calcium channel blocking agents include: therapy of angina pectoris (vasospastic angina and chronic stable angina); treatment of cardiac arrhythmias, particularly supraventricular tachyarrhythmias; treatment of hypertension; and correction of the hemodynamic abnormalities present in a condition known as hypertrophic cardiomyopathy. Finally, this group of drugs provides an invaluable research tool for both basic and clinical scientific investigation.

The history of the development of one of the calcium channel blocking agents, nifedipine, is of interest and serves to highlight the difficulties with the current drug regulatory process in the United States. Nifedipine was synthesized in Germany in 1968. Clinical investigation with the agent began in Germany in 1971 and eventually in 1975 nifedipine was approved as a general prescription item in that country. Between 1975 and 1980, 46 additional countries approved the use of nifedipine so that it is now available in a total of 47 nations. (Refer to Table 6 for a complete listing of the dates of approval of nifedipine in various countries).

Similarly, another calcium channel blocking agent, verapamil, which has profound clinical effectiveness in the emergency treatment of paroxysms of supraventricular tachycardia is an approved drug currently being administered in many countries throughout the world. It is available both in an intravenous and oral form.

Antiarrhythmic Agents

The second group of important new cardiovascular agents includes the antiarrhythmic drugs. One current classification of the various standard and investigational antiarrhythmic agents is provided in Table 2. These drugs offer an important life-saving measure to the 400,000 - 500,000 persons who suffer sudden cardiac death in the United States annually. These individuals succumb to a syndrome characterized by death usually within 24 hours when such an event was an unanticipated occurrence (representing a major alteration in the individual's usual state of health exclusive of deaths due to accidents or suicide). The vast majority of patients who suffer sudden cardiac death exhibit ventricular fibrillation which is an ineffective cardiac rhythm resulting in inadequate circulation of blood. Due to prompt cardiopulmonary emergency techniques in a number of centers around the United States, such patients are

now resuscitated in large numbers. When such a fatal arrhythmic occurs in the absence of an acute myocardial infarction, there is approximately a 30% chance of a recurrent fatal arrhythmia occurring within the next 12 months if no appropriate interventions are made.

Since one cannot at present predict which of the many antiarrhythmic agents will be effective in an individual patient, it is necessary to screen a large number of drugs to ascertain which ones are effective and produce the least number of troublesome side effects. Techniques for assessing drug efficacy include ambulatory monitoring, exercise testing, and electrophysiologic stimulation. This is a time-consuming task requiring heavy personnel commitments. A large number of forms currently required by the regulatory commission for monitoring investigational antiarrhythmics adds further to this task and in the opinion of many physicians serve to limit ready access to these valuable antiarrhythmics for the large number of patients who require them. In addition to the rather select population suffering from sudden cardiac death discussed above, there are vast numbers of individuals in this country requiring treatment with such antiarrhythmic agents for symptomatic ventricular arrhythmis but who do not have a past history of sudden cardiac death.

Beta Adrenergic Blocking Agents

The beta adrenergic blocking agents represent another important new class of cardiovascular drugs. The classification of adrenergic receptors in the human body is as follows: alpha 1 - stimulation causes constriction of blood vessels; alpha 2 - stimulation causes a decrease in sympathetic tone centrally, (i.e. from the brain); beta 1 - stimulation causes an increase in heart rate and force of heart contraction; beta 2 - stimulation results in dilatation of blood vessels and bronchial musculature and modulation of blood sugar levels. Compounds which block such receptors have been developed. The beta adrenergic

blockers have been divided into those compounds which non-specifically block both beta 1 and beta 2 receptors and those agents which specifically block beta 1 receptors. Table 3 compares many of the beta adrenergic blocking agents and emphasizes the concept of cardioselectivity (selective capacity to block beta 1 receptors) and their relative strengths versus the index compound propranolol. Additional important factors worth noting when comparing various beta adrenergic blocking agents include the duration of action and potential side effects. It would be advantageous to have several agents available in this country because of the variation in patient responses to beta blockers both in terms of clinical efficacy and adverse effects.

It is important to note that the beta adrenergic blocking agents represent another group of compounds which are effective in a number of cardiovascular disease states. Although the reference compound propranolol has been approved for many of these conditions (e.g. angina pectoris, hypertension, cardiac arrhythmias, migraine prophylaxis, treatment of pheochromacytoma and hypertrophic cardiomyopathy), the other approved beta adrenergic blocking agents are available for a much more restricted list of indications: Metoprolol - hypertension; Nadolol - hypertension and angina pectoris. This probably is a result of the requirement that each new beta adrenergic blocking agent be proven efficacious for each of the conditions for which propranolol is now standard therapy. This is a time-consuming process and delays approval of new beta adrenergic blocking agents for multiple indications.

Antihypertensive Agents

The new antihypertensive agents represent an additional class of compounds offering clinical promise for improved health care in this country. Hypertension is a widespread disease affecting millions of Americans. Unfortunately it remains a "silent" disorder until significant target organ damage is present

(stroke, myocardial infarction, heart failure, renal failure). Intervention trials have shown that appropriate diagnosis and early therapy of hypertensive patients can improve morbidity and mortality from this disorder. The classes of new hypertensive agents include: 1) New beta adrenergic blocking agents - metoprolol, nadolol, 2) new alpha-adrenergic blocking agents - prazosyn, 3) new alpha-2 receptor agonists (stimulators) - Clonidine, 4) new vasodilators - minoxidil and calcium channel blocking agents, 5) converting enzyme inhibitors - captopril (recently approved for refractory hypertension but not yet approved for congestive heart failure for which it is also probably effective). 6) new diuretics - metolazone.

Implications of Pharmaceutical Innovations

What are the implications of this ever expanding important cardiovascular pharmacologic armamentarium? There are three aspects of the current situation which deserve comment. First, a widespread educational campaign is necessary to alert the population at large, medical students, and practicing physicians to the indications and possible adverse effects of the many new drugs which are about to become available. Dosing requirements and important drug interactions should be stressed to medical health care professionals. The practicing physician relies on review articles in the medical literature (see Appendix I for example of a recent review on calcium channel blocking agents), other physicians, and educational symposia for maintaining a current fund of medical knowledge. There is a need for innovative educational techniques and sources for making pertinent new information available to the busy practicing physician in a simple and efficient manner. Such an educational campaign is necessary for maintenance of high standards of health care delivery when large numbers of potent medicines become more generally available.

Second, with the increasing number of drugs coming on to the market, the number of potential drug interactions rises in a fashion which cannot be predicted a priori. Long term careful drug surveillance techniques are necessary to detect such interactions (as has recently been discovered between digoxin and quinidine, two standard agents which large numbers of patients have taken in combination for many years). In order to simplify physician access to known or suspected drug interactions, a central repository of such valuable drug information should be established. One potential central base for such a repository might be the National Library of Medicine. Regional computer links throughout the United States could provide the mechanism for access to and the updating of such a data base.

Thirdly, the current regulatory process, although highly effective in preventing unsafe and unproven medicines from reaching the consumer market does so at the expense of a reasonable time course for new drug approval and utilizes a cumbersome structure for data collection and analysis. Patients in need of investigational agents have limited access to them, and in several cases undergo needless suffering and even death because of this process. Because many of the new drugs are more readily available outside the United States, some patients travel to foreign countries where they receive medicines which are still investigational in the United States.

Proposed Reforms

In order to rectify these matters, we should rely more heavily on data obtained in studies performed outside the United States, provided that a panel of scientific experts in this country has confirmed the reliability of specific foreign laboratories. Since individual clinical centers throughout the United States can only study a limited number of patients only a weak statistical statement can be made. By pooling in a cooperative manner, the

data collected at multiple centers throughout the United States a much more powerful statistical statement can be made about a drug's efficacy and safety (See Appendix II for an example of a study utilizing pooled data from multiple investigating centers). The National Institute of Health is currently funding one such study entitled "Multicenter Investigation for the Limitation of Infarct Size (MILIS)" which is designed to test the effects of a number of medicines on limiting the size of a myocardial infarction (heart attack).

Simplification of data collection techniques is necessary to unburden physicians currently treating patients with investigative agents. This could at least in part be accomplished by eliminating repetitive points of data collection and utilizing pooled information from reputable foreign sources and multiple United States investigative centers.

Summary

In summary, important points for consideration and potential legislation include 1) enhanced educational sources and techniques, 2) optimal use of existing technology for storage and retrieval of information on available agents, 3) modification of the drug regulatory process emphasizing shortening the time required for approval of a new drug.

Interest on the part of Congress in the "promises and problems" relating to pharmaceutical innovation is encouraging evidence of governmental responsiveness to the changing needs of patients and physicians in this country. Legislative reform which will be generated as a result of joint hearings such as this one today, is urgently needed to ensure that Americans continue to lead healthy, productive lives with minimal suffering due to illness. Thus, the advent of the "breakthrough era" in drug therapy provides a unique opportunity for the development of both new medical and governmental practices.

TABLE I

CALCIUM CHANNEL BLOCKING AGENTS

1. Nifedipine
2. Verapamil
3. Diltiazem
4. Perhexiline
5. Lidoflazine
6. Prenylamine

TABLE 2

CLASSIFICATION OF ANTIARRHYTHMIC AGENTS

SINGH ET AL 1980*

1. MEMBRANE STABILIZATION ($\downarrow G_{NA}$)

QUINIDINE	APRINDINE	AJMALINE
PROCAINAMIDE	*MEXILITENE	DISOPYRAMIDE
*PHENYTOIN	*TOCAINIDE	ETHMOZIN
*LIDOCAINE	*ENCAINIDE	* $\uparrow G_K$

II. ADRENERGIC BLOCKADE

PROPRANOLOL	PINDOLOL	ACEBUTOLOL
OXPRENOLOL	PRACTOLOL	
ALPRENOLOL	ATENOLOL	

III. INCREASE APD

AMIODARONE
BRETYLIUM

IV. SLOW CHANNEL BLOCKADE

VERAPAMIL

* MODIFIED FROM SINGH BN, COLLETT JT, CHEW CYC. "NEW PERSPECTIVES IN THE PHARMACEUTICAL THERAPY OF CARDIAC ARRHYTHMIAS" PROG CARDIOVASC DIS 22:243, 1980.

TABLE 3

BETA-BLOCKING DRUGS

Dosages and Pharmacology of Beta-Blocking Drugs

Generic Name / Trade Name	Comparative Beta-Blocking Activity	Cardio-selectivity	Average I.V. Dose (mg/kg /body wt)	Average Oral Dose (mg/day)	T½ (h)	Active Metabolite Identified	Instrinsic sympathomi-metic activity	Membra Stabil zing activi
Propranolol Inderal	1.0	–	0.15	80-320	2-3	Yes	0	+
Practolol Eraiden	0.3	+	0.4	400-1200	5-13	No	+	0
Alprenolol Aptin	1.0	–	0.2	400	2-3	Yes	+	+
Pindolol Visken	4.0	–	0.15	20-40	3-4	No	+	+
Acebutolol Sectral	0.3	+	0.4	600-1200	2-3	Yes	+	+
Metoprolol Lopressor	1.0	+	0.15	100-450	3-4	No	0	0
Oxprenolol Trasicor	1.0	–	0.2	160-300	1-2	No	+	+
Atenolol Tenormin	0.5	+	–	100-300	5-7	No	0	0
Nadolol - gard	1.0	–	–	40-240	16-18	No	0	0
Timolol	6.0	0					0	0

TABLE 4

NEW INOTROPIC AGENTS

1. Amrinone
2. Pirbuterol
3. Prenalterol
4. Salbutamol

TABLE 5

DIURETICS

1. Ticrynafen
   (removed from market)
2. Metolazone
3. Piretanide
4. Amiloride

TABLE 6

WORLDWIDE EXPERIENCE

Nifedipine was first introduced in Germany in January, 1975 and is currently marketed in forty-seven countries (Table I). Worldwide, about four million patients have been treated with nifedipine.

TABLE I - COUNTRIES IN WHICH NIFEDIPINE IS CURRENTLY MARKETED

COUNTRY	YEAR OF INTRODUCTION	COUNTRY	YEAR OF INTRODUCTION
Germany	1975	Hong Kong	1977
Austria	1975	Chile	1977
Argentina	1975	England	1977
Uruguay	1975	Lebanon	1977
Switerzerland	1975	Ireland	1977
Portugal	1975	South Korea	1977
Singapore	1975	Peru	1978
Spain	1976	Venezuela	1978
Mexico	1976	Luxemburg	1978
Colombia	1976	Belgium	1978
Egypt	1976	Jordan	1978
Philippines	1976	Syria	1978
South Africa	1976	Poland	1978
Italy	1976	Hungary	1978
Brazil	1976	Romania	1978
Japan	1976	Cyprus	1978
Czechoslovakia	1976	France	1979
Malta	1976	Taiwan	1979
Kuwait	1976	Iran	1979
Malaysia	1976	Israel	1979
Bahrain	1976	Denmark	1979
Abu Dhabi	1976	Pakistan	1979
Turkey	1977	Kenya	1979
		Sweden	1980

Nifedipine has been the object of extensive pre-clinical and clinical study for well over a decade. Over 900 references in the world scientific literature discuss nifedipine's efficacy, safety, and mechanism of action. There have been eight major symposia which have focused on the pharmacology and clinical use of nifedipine in the management of angina pectoris as well as other cardiovasculor diseases.

The worldwide clinical experience with nifedipine is extensive. The results of clinical research and post-marketing surveillance, involving over 14,000 patients has demonstrated the efficacy of nifedipine in the treatment of angina pectoris. Evaluation of safety in more than 11,500 patients has shown nifedipine to be well tolerated and safe, with

Data provided by Thomas D. Robinson, M.D., Senior Associate Medical Director, New Drug Development, Pfizer Pharmaceuticals, Pfizer, Inc., 235 E. 42nd Street, New York, New York 10017

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Calcium Channel Blocking Agents in the Treatment of Cardiovascular Disorders. Part I: Basic and Clinical Electrophysiologic Effects

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Calcium ions play an important role in the cardiovascular system. They are involved in electrophysiologic processes, link excitation to muscular contraction, control energy storage and utilization, and constrict vascular smooth muscle in coronary and systemic arteries. A new group of pharmacologic agents that block the passage of calcium ions across cell membranes has been developed. These agents act during the slow inward current of cellular depolarization. The most extensive clinical experience has been obtained with four of these agents: verapamil, nifedipine, perhexiline, and diltiazem. Verapamil, which has profound electrophysiologic effects on the slow inward current, is emerging as a valuable antiarrhythmic agent. Re-entrant supraventricular arrhythmias, such as paroxysmal supraventricular tachycardia, are particularly amenable to treatment with intravenous verapamil. Preliminary trials of long-term therapy with oral verapamil for control of atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia suggest that this agent is effective for therapy of these arrhythmias.

CALCIUM IONS (Ca^{++}) play critical roles in a number of biologic processes: They are involved in the maintenance of hemostasis, a broad array of enzymatic reactions, the metabolism of bone, electrical activation of various excitable cells, and the coupling of electrical activation to cellular secretion and muscular contraction (1-9). In the cardiovascular system, Ca^{++} is of great importance for several physiologic events. In myocardial cells and specialized automatic and conducting cells in the heart, Ca^{++} is involved in the genesis of the cardiac action potential, links excitation to muscular contraction, and controls energy storage and utilization (Figure 1)(1). The lumina of coronary and systemic arteries may be altered by changes in smooth muscle tone induced by the movement of Ca^{++} across the membranes of smooth muscle cells.

During the past 2 decades a number of pharmacologic agents that block the movement of Ca^{++} across cell membranes have been developed. These agents will have a major impact on the therapy of numerous cardiovascular disorders, including cardiac arrhythmias, myocardial ischemic states, hypertension, and hypertrophic cardiomyopathy. Application for approval of these drugs is currently pending in the United States, but the drugs are not available at this time. The purpose of this review is to describe the pharmacology and clinical results with the newly developed Ca^{++} channel blocking agents in various cardiovascular disorders.

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Role of Calcium Ion Fluxes in the Heart

ACTION POTENTIAL OF CARDIAC CELLS

An understanding of the role of Ca^{++} fluxes in cellular electrophysiology requires an appreciation of the electrical activity of cardiac cells. The changes in transmembrane potential that occur during the action potential of cardiac cells are divided into five phases: phase 0, rapid depolarization; phase 1, early repolarization; phase 2, plateau; phase 3, rapid repolarization; and phase 4, diastole (Figure 2A). The shape of the action potential varies among the different types of cardiac cells (10, 11). Cells in the sinoatrial (SA) and atrioventricular (AV) nodes (Figure 2A) depolarize at a much slower rate than do cells in Purkinje fibers or atrial or ventricular contractile fibers (Figure 2B).

The resting transmembrane potential during phase 4 represents the net effect of the cell actively maintaining a high intracellular K^+ concentration. In addition the cardiac cell actively extrudes Na^+ from its interior (10) so that the extracellular Na^+ concentration ($[Na^+]_o$) greatly exceeds the intracellular $[Na^+]_i$. During this phase of the action potential the interior of the cell is about 90 mV negative to the exterior, and the conductance of the cell membrane for K^+ is greater than that for Na^+ (12).

FAST INWARD CURRENT

During phase 0 when cardiac cells are depolarized, the membrane conductance for Na^+ rapidly increases, resulting in the fast inward current. This current is dependent on the extracellular $[Na^+]$ and can be blocked by tetrodotoxin, a toxin produced by the Japanese puffer fish; elevated extracellular $[K^+]$; and agents with local anesthetic activity (13). The fast inward current can be described in terms of activation ("m") and inactivation gates ("h") (10, 12, 14). As Na^+ ions rush into the cell through open "m" gates, the transmembrane potential becomes less negative (inside with respect to outside) and the "h" gates close, thereby terminating the fast inward current.

SLOW INWARD CURRENT

When the cell has been depolarized from −90 mV to about −40 mV, a second inward current, termed the slow inward current, develops (12, 13, 15-17). The rates of activation and inactivation of the slow inward current,

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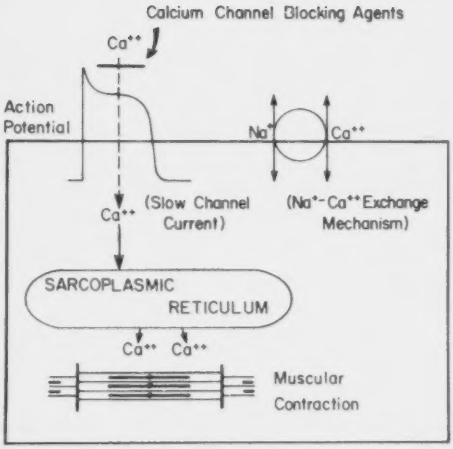

Figure 1. Schematic summary of the role of Ca^{++} in processes of excitation and contraction in myocardial cells. Elevation of myoplasmic [Ca^{++}] via release from the sarcoplasmic reticulum and entry via the slow inward current and Na^{+}-Ca^{++} exchange mechanism results in muscular contraction. Entry of Ca^{++} via the slow inward current during the plateau phase of the action potential is inhibited by Ca^{++} channel blocking agents. Possible additional sites of inhibition of Ca^{++} fluxes by Ca^{++} channel blocking agents are being explored.

which contributes to the plateau phase (phase 2) of the cardiac action potential, are several orders of magnitude slower than those of the fast inward current (13, 15, 18). The slow inward current can be activated at levels of membrane voltage that would ordinarily inactivate the fast inward Na^{+} current (13, 18, 19-21) and reaches its maximum value when membrane potential is in the range of −20 to 0 mV (18). The major ionic species traversing the cell membrane during the slow current is Ca^{++} (13), but when the extracellular [Ca^{++}] is lowered or reduced to zero, Na^{+} become the predominant charge carriers during the slow inward current (22-24). The contribution of Na^{+} to the slow inward current under normal conditions is complex and differs among species and cardiac tissues (25). The membrane channels carrying the slow inward current—that is, the so-called "slow channels"—have been estimated by Reuter (13, 19) as being 100 times more selective for Ca^{++} than for Na^{+} or K^{+}, justifying the use of the term "calcium channel."

The exact nature of the many ionic fluxes that take place during the cardiac action potential is only partially understood (10, 11, 13, 26-28), but the principal features of the fast and slow inward currents are summarized in Table 1. Although the two currents are said to flow through separate fast and slow "channels," these "channels" have not yet been identified as distinct anatomic structures. In addition, much of the information listed in Table 1 has been obtained from experiments conducted in isolated in-vitro preparations exposed to nonphysiologic conditions (29), and their relevance to intact organisms needs further elaboration.

The slow inward current is believed to pass through membrane channels distinct from those used by the fast inward current. Such channels may be thought of as specific protein macromolecular structures that traverse the lipid bilayer at various locations (30, 31). Divalent cations with ionic radii similar to that of Ca^{++}, such as Ba^{++} or Sr^{++}, can pass through the calcium channel, while ions whose radii differ markedly from that of Ca^{++}, such as Mn^{++}, Co^{++}, Ni^{++}, and La^{+++}, can block these channels and inhibit passage of Ca^{++} (30-32). Although these ions may be considered to be Ca^{++} channel blocking agents, clinical interest in their use is limited in view of their potent general effects.

Action potentials from cells in atrial and ventricular contractile tissues, specialized intracardiac conduction system, and distal AV nodal regions depend on both the fast and slow inward currents. Pacemaker cells of the SA node and cells in the proximal regions of the AV node have slowly rising action potentials and a reduced rate of conduction and are activated largely by the slow inward current. Such "slow responses" may be observed in other cardiac cells under abnormal conditions such as ischemia, hypoxia, and exposure to catecholamines (11).

MODULATION OF SLOW INWARD CURRENT; ROLES OF CYCLIC AMP AND ATP

Beta-adrenergic agonists such as isoproterenol, epinephrine, cyclic AMP, and dibutyryl cyclic AMP all increase the magnitude of the slow inward current (15, 25, 29, 33-37) (Table 1), while β-adrenergic blocking agents reduce Ca^{++} influx (1, 22, 25). The mechanisms by which catecholamines exert their effects have been extensively investigated. Reuter and Scholz (36) have shown in isolated Purkinje fibers that enhancement of the slow inward current by catecholamines is due to an increase in Ca^{++} conductance through the slow channel without any alterations in the kinetics of the slow inward current or selectivity of the slow channel. Schneider and Sperelakis (22, 29) have confirmed this effect of catecholamines in isolated perfused guinea pig hearts, showing that the addition of catecholamines to ventricular myocardium rendered inexcitable by exposure to high [K^{+}] rapidly restored waveforms that had a slow activation time and a contour similar to the plateau phase of the cardiac action potential. Similar results were obtained with methylxan-

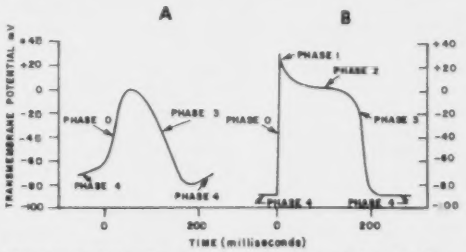

Figure 2. Typical action potentials recorded from cells in the sinoatrial node (*A*) and ventricular myocardium (*B*). Note the slower rate of rise and smaller amplitude of the sinoatrial node action potential.

Table 1. Characteristics of Fast and Slow Inward Currents of Cardiac Action Potential

	Fast	Slow
Ionic species involved	Na^+	Ca^{++} (Na^+)
Maximal rate of depolarization, *V/s*	Rapid (100–1000)	Slow (1–20)
Time constant of inactivation, *ms*	Rapid (1–2)	Slow (50–200)
Threshold of activation, *mV*	−60 to −70	−30 to −40
Extracellular ion of importance	Na^+	Ca^{++}
Current flow decreased or eliminated by	Tetrodotoxin, ↑extracellular [K^+], local anesthetics	Mn^{++}, verapamil, nifedipine, perhexiline, diltiazem
Current inactivated by sustained depolarization to −50 mV	+	−
Current flow increased or prolonged by	veratridine	Catecholamines, cyclic AMP
Cellular localization		
Sinoatrial node	−	+
Atrial myocardium	+	+
Atrioventricular node		
Proximal	−	+
Distal	+	+
His-Purkinje system	+	+
Ventricular myocardium	+	+

thines (for example, caffeine), histamine, and angiotensin II. Addition of cyclic AMP or dibutyryl cyclic AMP also induced the "slow response" but with a slightly delayed time course.

A model of the slow channel that has been proposed to explain these results is shown in Figure 3 (13, 29). There are two separate gates in the slow channel: One gate is voltage-dependent and may be completely open ("d") or closed ("f"); a second gate ("g") is less dependent on voltage but may open to varying degrees depending on anatomic modification. This can be accomplished by substances such as cyclic AMP that are capable of modifying the ionic currents during the cardiac action potential (38). An increase in cyclic AMP levels could occur as a consequence of the stimulation of adenylate cyclase by catecholamines, or by the inhibition of the phosphodiesterase that degrades cyclic AMP (methylxanthines). Cyclic AMP may activate a protein kinase that catalyzes a critical phosphorylation reaction at the inner gate of the slow channel (29, 35, 36, 39, 40). The important role played by cyclic AMP is suggested by the oscillations in cyclic AMP levels that occur during the cardiac cycle, with the peak occurring midway through the rise in tension (41, 42). Muscarinic agonists such as acetylcholine lead to an increase in cyclic GMP that opposes the effects of cyclic AMP and causes a reduction in the slow inward current (43, 44). The ultimate magnitude of the slow inward current is determined by the number of slow channels open and by the extent of their opening (25, 29). The channels are opened by depolarization of the cell membrane to a threshold voltage (activation of the voltage-dependent gate). The extent of opening of the full Ca^{++} channel is determined by the availability of cyclic AMP to promote phosphorylation of a protein at the inner surface of the membrane (22, 29).

In addition to cyclic AMP, interventions that alter cellular energy stores have been found to affect the slow inward current. Thus, in the isolated heart slow electrical responses can be abolished and electromechanical uncoupling can be produced by ischemia, anoxia, cyanide, dinitrophenol, or valinomycin (an uncoupler of oxidative phosphorylation) (44, 45). Presumably the reduced adenosine triphosphate (ATP) concentration of the myocardium abolishes the slow inward current (46, 47). It has been proposed that ATP may increase the slow inward current by chelating intracellular Ca^{++} adjacent to the sarcolemma, thereby ensuring a large electrochemical driving force for the inward Ca^{++} current during the plateau phase of the action potential (48). In addition, ATP probably plays a central role in the phosphorylation of the inner membrane component of the slow channel illustrated in Figure 3 (29).

Na^+—Ca^{++} EXCHANGE

Calcium ion fluxes across the myocardial cell membrane may also occur in exchange for Na^+ (49). Calcium ion influx is believed to occur via a Na^+—Ca^{++} carrier mechanism separate from the slow channel described above. The magnitude of such Ca^{++} fluxes is dependent on the relative intracellular and extracellular [Na^+] (50). Although the precise stoichiometry is unclear, recent evidence suggests that the Na^+—Ca^{++} exchange is electro-

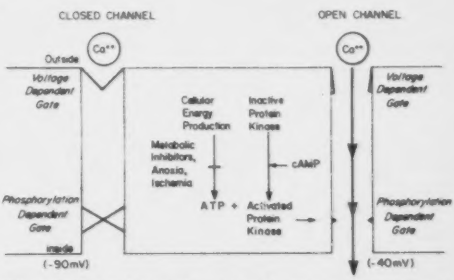

Figure 3. Model of the slow inward calcium channel. The channel is opened by depolarization of the cell to a threshold voltage, while the extent of opening is controlled by activation of a protein kinase at the phosphorylation-dependent gate.

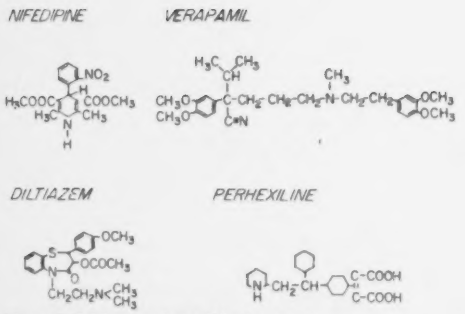

Figure 4. Calcium ion channel blocking agents.

genic and dependent on membrane potential (51, 52). This exchange is not energy-requiring, but ATP greatly influences the process by altering the affinity of the carrier for Na^+ or Ca^{++}, or both (53). In addition to decreasing the magnitude of Ca^{++} influx via the slow inward current, La^{+++} has been shown to inhibit $Na^+ - Ca^{++}$ exchange in cardiac membrane vesicles (54). The relative magnitude and functional importance of Ca^{++} fluxes via the slow inward Ca^{++} channel and $Na^+ - Ca^{++}$ exchange mechanism are currently being investigated.

Specific Blockade of the Slow Channels

A number of agents that inhibit the slow inward current (Figure 4) are now available and are of great potential value in the treatment of numerous cardiovascular disorders. Most clinical experience has been obtained with four drugs: verapamil, nifedipine, perhexiline, and diltiazem. Verapamil, which has profound electrophysiologic effects, is emerging as a valuable antiarrhythmic agent. Nifedipine, a potent vascular spasmolytic agent, may be of value in a number of disorders in which vasoconstriction plays a role. We now focus attention on the electrophysiologic effects of slow channel blockade; the clinical consequences of slow channel blockade on excitation-contraction coupling are discussed in Part II in this issue (pp. 886-904).

The blocking agents have also been termed "calcium antagonists" (1). As Katz and Reuter have pointed out (55), however, these agents are more appropriately termed "calcium channel blockers," since it appears their predominant action is antagonism of Ca^{++} fluxes at specific sites such as cellular membranes (55). In addition it is probably incorrect to consider these drugs as specific competitive Ca^{++} channel blockers (13, 25, 56). As summarized by Henry (56), the "calcium blocking" compounds vary markedly in chemical structure, and their inhibitory effects on the slow inward current are not always completely corrected by increases in external $[Ca^{++}]$ or mimicked by reduction in external $[Ca^{++}]$. The drugs vary in their electrophysiologic effects on the fast and slow inward currents. Thus, diltiazem in a concentration somewhat greater than that capable of blocking the slow inward current has also been shown to inhibit the fast inward current and reduce the rate of rise of the action potential (57). Nifedipine does not appear to modify the fast inward current. Some authors have postulated that nifedipine reduces the number of slow inward channels in a dose-dependent fashion without affecting the kinetics of the remaining operative channels (56, 58, 59). In contrast, verapamil and its methoxyderivative D-600 modify the kinetics of the slow current by altering the rates of activation, inactivation, and recovery of the slow channels (56, 60-62). Verapamil, but not nifedipine, is also capable of blocking an outward current carried by K^+ that occurs during repolarization (56, 63, 64).

In view of the heterogeneity of structure and varying electrophysiologic and vascular actions of these compounds, it is premature to ascribe all of their effects to "calcium channel blockade" (25). An interesting aspect of the pharmacology of verapamil and D-600 has been described (65-67). The (−) optical isomers possess potent Ca^{++} blocking and negative inotropic properties, whereas the (+) isomers are much less potent Ca^{++} channel blockers. The (+) isomers may also block the fast inward current (67, 68). Many of the laboratory and clinical studies with verapamil have used a racemic mixture. It is unclear whether any of the other drugs shown in Figure 4 have these differential effects of their optical isomers. The differences among the calcium blockers justify consideration of different subgroups of agents. There may be at least two groups of agents distinguishable: agents that prevent activation of slow channels (for example, nifedipine), and agents that alter the kinetics of activation and recovery from inactivation of slow channels (for example, [−] verapamil) (56, 58). In addition, the sensitivity of Ca^{++} channels to pharmacologic agents may vary in cells from different tissues, as has been shown for both α- and β-adrenergic receptors. Rowland and colleagues (69), for example, have proposed that there may be either a qualitative or quantitative difference in the response of the slow channels in vascular smooth muscle cells and AV nodal cells to Ca^{++} channel blocking agents.

Additional points worthy of consideration are the possible effects of Ca^{++} channel blocking agents on outward (repolarizing) currents that occur later in the action potential. As summarized by Coraboeuf (10), these late outward currents are carried predominantly by K^+ and are believed to pass through K^+ "channels" in the membrane. Because there is evidence that an elevated intracellular $[Ca^{++}]$ increases the late outward K^+ conductance (25, 70), possibly Ca^{++} channel blocking agents may reduce the late outward current by lowering intracellular Ca^{++} levels (62). Finally, preliminary studies suggest that the organic Ca^{++} channel blocking agents do not affect the Na^+-Ca^{++} exchange mechanism discussed above (71).

Effects of Calcium Channel Blocking Agents on Electrophysiologic Properties of the Heart

EFFECTS ON SINUS NODE, AV NODE, AND ATRIA

Properties common to both specific organic Ca^{++} channel blocking agents and inorganic blocking agents such as Mn^{++} or La^{+++} include a depressant effect on the rate of sinus node discharge (negative chronotropic

effect) and inhibition of conduction velocity through the AV node (negative dromotropic effect) (72). These effects are easily demonstrated by injections of the agents directly into the arteries supplying the SA and AV nodes (73-76). In addition, these effects can be demonstrated in isolated tissue preparations perfused with Tyrode's solution, containing varying concentrations of the blocking agents (77, 78). The inhibitory effects do not appear to be mediated via the autonomic nervous system because they occur in the presence of autonomic blockade with atropine and propranolol (72). However, β-adrenergic agonists that increase the magnitude of the slow inward current by elevation of cyclic AMP can reverse these inhibitory properties (79). Thus, epinephrine has been shown to restore SA nodal automaticity in verapamil-treated fibers (78). The upper and middle sections of the AV node have diminished amplitude and upstroke velocity of action potentials exposure to 4.4×10^{-7} M of verapamil (78). The effective refractory period of the AV node is prolonged, and conduction velocity is suppressed by verapamil and can be restored by exposure to catecholamines. Prolongation of AV nodal refractoriness and slowing of conduction by verapamil prevent the experimental induction of re-entrant AV nodal tachycardia in isolated rabbit atrial preparations, an action that may provide the theoretical basis for its clinical effectiveness in controlling supraventricular rhythm disturbances dependent on re-entry involving the AV node (78).

The relative potencies of the negative chronotropic and negative dromotropic properties of the calcium blockers depend on the dose and route of administration. Using intra-arterial injections of blood-perfused isolated SA and AV node preparations, equal doses of nifedipine and (±) verapamil were found to possess equal negative chronotropic properties (73-76). However, (±) verapamil was only one half as potent as nifedipine in slowing AV nodal conduction. Diltiazem and perhexiline in that order were much less potent than either nifedipine or verapamil in their effects on the SA and AV nodes. However, different results were obtained in an in-vivo model in which autonomic nervous system influences were intact. In chronically instrumented conscious dogs, intravenous verapamil (0.1 to 0.4 mg/kg body weight) and nifedipine (0.01 to 0.04 mg/kg body weight) caused equal reductions in blood pressure and similar increases in heart rate (80). However, only the verapamil-treated dogs had prolongation of AV conduction, which led to 2° AV block in some instances. On the other hand, nifedipine in this dose range had no discernible effect on AV conduction. Using His bundle recording techniques and programmed atrial pacing, Padeletti and colleagues (81) studied the electrophysiologic effects of 20 mg of nifedipine sublingually in resting, nonsedated patients. The intrinsic automatic function of the SA node and AV nodal and His Purkinje conduction were unchanged after nifedipine administration. Heart rate was increased, however, which was presumed secondary to reflex sympathetic activity.

Although both nifedipine and verapamil can prolong the atrial refractory period, the dose response curve is much less steep for nifedipine than for verapamil (80), and the (−) isomer of verapamil is nearly 10 times more potent than the (+) isomer in this regard (82). The excitability of atrial fibers is depressed by 2×10^{-5} M verapamil but not by 1×10^{-6} M nifedipine (80). Both (±) verapamil (3×10^{-5} M) and diltiazem (2.2×10^{-5} M) lengthen the duration and slow the maximal rate of rise of the atrial action potential; nifedipine (2.9×10^{-6} M) has no effect on these variables (57).

Pronounced differences between nifedipine and verapamil are apparent when simultaneous effects on coronary blood flow and atrioventricular conduction of single injections of 0.3 to 30 μg are ascertained (83). Verapamil increases blood flow through the AV node and prolongs AV nodal conduction time in the same dose range, whereas any given dose of nifedipine in the above range causes a 10-fold greater increase in AV nodal artery flow than in AV nodal conduction time. In hearts deprived of sympathetic control, however, nifedipine has been shown to prolong AV nodal conduction as well as increase coronary blood flow (84).

In an attempt to elucidate the role of slow response in atrial arrhythmias, Hordof and colleagues (85) used standard microelectrode techniques to record action potentials of diseased human right atrial fibers obtained in the course of cardiac operations. Action potentials from fibers removed from dilated atria with a propensity to atrial arrhythmias and prolonged P-wave durations had resting membrane potentials in the range of − 50mV. These action potentials were of low amplitude, slowly rising, and appeared to be "slow channel responses" (86). They differed from action potentials recorded in fibers obtained from less diseased atria which had a rapid upstroke indicative of "fast channel responses." Verapamil markedly depressed the slow channel-dependent action potentials but only affected the plateau phase of the fast channel-dependent action potentials. Because the slowly conducting action potentials from the diseased atria could lead to reentry, their depression by verapamil provides further rationale for the use of that drug in re-entrant paroxysmal supraventricular arrhythmias.

EFFECTS ON VENTRICULAR ELECTRICAL ACTIVITY

The effects of Ca^{++} channel blocking drugs on ventricular tissues and ventricular arrhythmias have also been examined. Kohlhardt and associates (87) studied the transmembrane Na^{+} and Ca^{++} currents during the action potential of isolated trabeculae from the right ventricle of cats. By means of a voltage clamp technique the membrane potential could be shifted from one level to another and held constant at a selected level by passage of current across the membrane. After eliminating the fast inward Na^{+} current by depolarizing the cell membrane, these investigators showed that the second inward current was dependent on the extracellular $[Ca^{++}]$ and could be markedly inhibited by 4.4×10^{-6} M verapamil. These inhibitory effects of verapamil were completely neutralized by a fourfold increase in extracellular $[Ca^{++}]$ from 2.2 mM to 8.8 mM. In contrast to these pronounced Ca^{++} channel blocking properties in ventricular tissues, (±) verapamil has had little effect on the fast inward

Na^+ current (77, 87). Purkinje fibers exposed to Na^+-free Tyrode's solution develop action potentials that are Ca^{++} dependent. Verapamil suppresses spontaneous and electrically stimulated rhythmic activity and depresses excitability in such fibers (77). These inhibitory effects of verapamil are blunted by an increase in extracellular $[Ca^{++}]$.

Nifedipine (10^{-6} M) does not affect the resting potential, rate of rise of the action potential, or excitability of isolated cat papillary muscles perfused with normal Tyrode's solution (59) but does depress the plateau phase of the action potential. Neither nifedipine nor (±) verapamil injected directly into the artery supplying isolated blood-perfused preparations of canine papillary muscles affects the automaticity of these ventricular fibers (88). However, as has been noted by Cranefield and coworkers (77) for Purkinje fibers exposed to verapamil, Ca^{++}-dependent action potentials (generated in preparations with a low external $[Na^+]$ from ventricular muscle of cats) are markedly inhibited by nifedipine. This inhibition is mediated by a reduction in the magnitude of the slow inward current without an alteration in its kinetics of inactivation or an alteration in its recovery from inactivation (58). In contrast to the resistance of ventricular automaticity to nifedipine and verapamil, Ten Eick and Singer (89) have shown that perhexiline maleate reduces both automaticity and conduction velocity in isolated specimens of rabbit ventricle.

Experimental ventricular arrhythmias resulting from manipulation of coronary blood flow appear to be responsive to slow channel blocking drugs (90). Kaumann and Aramendia (91) found that in contrast to β-adrenergic blockade, pretreatment with verapamil prevented ventricular fibrillation in dogs undergoing coronary artery ligation; the (−) isomer being several times more potent than the (+) isomer in preventing fibrillation (92). The threshold for electrical induction of ventricular fibrillation in dogs is raised by pretreatment with (±) verapamil or another Ca^{++} channel blocking agent, prenylamine (93, 94). Whether slow-response action potentials play a role in the genesis of ventricular arrhythmias that complicate acute myocardial infarction is uncertain. The clinical value of Ca^{++} channel blocking agents in controlling such arrhythmias is also disputed (95-99).

TRIGGERED REPETITIVE ACTIVITY

In addition to spontaneous phase-4 depolarization resulting in pacemaker potentials, repetitive activity can be "triggered" by a preceding depolarization (triggered repetitive activity) (100). Such activity has been identified in normal simian mitral valve leaflet tissue (101), in a human anterior mitral valve leaflet obtained from the heart of a recipient of a cardiac transplant (102), in fibers of rat atrial pectinate muscle (103) and crista terminalis, in fibers in the region of the coronary sinus in dogs (104), in canine Purkinje fibers exposed to Na^+-free Ca^{++}-rich solutions (105), in cardiac fibers poisoned with ouabain (105-108), in perfused Purkinje fibers, and in mitral valve tissue exposed to epinephrine (86, 100). The precise electrophysiologic mechanisms that produce triggered automatic rhythms have not yet been completely elucidated but appear to be related to oscillations of the membrane potential during the later phase of repolarization (100). Cranefield (11, 100) has summarized the relation of such oscillatory activity to arrhythmias and the evidence suggesting a role for a transient inward current in their genesis. Kass and coworkers (109) have presented evidence that this transient inward current is conducted via a different membrane ionic pathway from that used by the slow inward current and is carried predominantly by ions other than Ca^{++}. The oscillatory activity, however, may be related to oscillatory release of Ca^{++} from overloaded intracellular stores (110). The Ca^{++} channel blocking compounds verapamil and D-600 can prevent or abort such triggered activity (100). This may in part explain verapamil's effectiveness in certain supraventricular rhythm disturbances (3, 102). It is uncertain whether clinically tolerated doses of verapamil have a beneficial effect on arrhythmias produced by digitalis intoxication (3, 100, 101, 111, 112).

Clinical Applications of Electrophysiologic Effects of Calcium Channel Blocking Agents

SINUS NODE FUNCTION

Because of experimental evidence indicating that verapamil (0.25 to 0.5 mg/kg body weight) may suppress latent pacemakers arising in the right atrium when the SA node is surgically excised, the drug should be used with caution in patients with pre-existing sinus node dysfunction (113). In addition there is clinical evidence suggesting that verapamil may markedly worsen abnormal baseline sinus node function (114, 115). Prolongation of sinus node recovery time by verapamil has been noted, an expected effect because cells in the SA node depend primarily on the slow Ca^{++} current for their action potential. No effects of verapamil on intra-atrial conduction have been found (69, 115-118).

AV NODE FUNCTION

In patients in sinus rhythm, acute administration of verapamil had no effect on the R-R, QRS, or Q-T_c intervals on the electrocardiogram (119, 120). Because of its ability to delay AV conduction, however, verapamil may prolong the P-R interval (115, 119). A number of studies using His bundle recordings have confirmed that this effect is due to delay in the AV node.

In a comparison of the effects of intravenous nifedipine (7.5 μg/kg) with those of verapamil (0.15 mg/kg body weight) on intracardiac conduction (69), both drugs caused a slight reduction in the cycle length of the sinus node, presumably due to reflex stimulation of the sympathetic nervous system. Nifedipine had no effect on AV conduction time (A-H interval), whereas verapamil caused a significant increase in the A-H intervals. Kawai and coworkers (120) recently showed in humans that whereas diltiazem and verapamil increased the effective and functional refractory periods of the AV node, nifedipine administration actually resulted in a decrease in these measurements. This is probably due to a reflex increase in sympathetic tone caused by a nifedipine-induced decline in systemic arterial pressure. The intrave-

nous administration of 10 mg of diltiazem in patients with ischemic heart disease prolonged the A-H interval (as did verapamil), and this increase was not affected by pretreatment with atropine. No changes in intra-atrial or intraventricular conduction times were observed (121).

ACCESSORY PATHWAYS

Programmed electrical stimulation studies in patients with accessory pathways have reported variable effects of Ca^{++} blocking drugs on the refractory period of the bypass tract (122, 123). One report suggests that bypass tracts capable only of retrograde conduction (concealed bypass pathways) are more sensitive to verapamil than are those that conduct in an antegrade direction (123). As emphasized by Spurrell and colleagues (122), verapamil is helpful in controlling circus movement tachycardias involving anomalous pathways but would not be expected to be beneficial in slowing the ventricular rate in atrial fibrillation during antegrade conduction over the bypass tract. Like digitalis, in some cases verapamil may actually shorten the effective refractory period for antegrade conduction over the bypass tract and thus cause harm in this situation (122, 124).

SUPRAVENTRICULAR ARRHYTHMIAS

Verapamil is the Ca^{++} blocking agent that has received the widest clinical application as an antiarrhythmic. The major role of verapamil lies in controlling supraventricular tachyarrhythmias (125-127), and most of the published experience has been with the intravenous method of administration. Nifedipine, perhexiline, and diltiazem have received limited clinical trials and have not been found to be as useful as verapamil for the treatment of supraventricular arrhythmias.

Verapamil can slow the atrial rate in sinus tachycardia and has been reported to convert some cases of junctional tachycardia to sinus rhythm (128). However, intravenous verapamil has been found to be most effective in rapidly terminating re-entrant paroxysmal supraventricular tachycardia (119, 125-133). Since conversion to sinus rhythm occurs in about 90% of cases within minutes of administration, intravenous verapamil is emerging as the drug of choice for this arrhythmia. In comparison, β-adrenergic blocking drugs are effective in only 50% to 60% of cases (134). Krikler and Rowland (135) have reported that 0.15 mg/kg body weight of intravenous verapamil terminated 195 of 199 cases of paroxysmal supraventricular tachycardia when the arrhythmia was due to re-entry within the AV node or via an accessory pathway. An equihypotensive dose of nifedipine failed to prolong AV conduction and did not exert an antiarrhythmic effect (69). Paroxysmal supraventricular tachycardia due to an ectopic atrial focus may be slightly less responsive to intravenous verapamil than re-entrant paroxysmal supraventricular tachycardia; in Krikler and Rowland's experience only six of nine cases of ectopic atrial tachycardia converted to sinus rhythm; the three nonresponding patients had AV conduction delay only after verapamil administration (126).

Singh and associates (126) have summarized the various changes in cardiac electrical activity by which paroxysmal supraventricular tachycardia may be terminated by intravenous verapamil. These include abrupt termination such as might be seen with carotid sinus pressure, a reduction in the ventricular rate followed by a short pause before reversion to sinus rhythm, AV dissociation with a junctional escape rhythm followed by sinus rhythm, transient atrial fibrillation followed by sinus rhythm, the occurrence of ventricular premature beats followed by reversion to sinus rhythm, and alternation of cycle length before appearance of sinus rhythm (136, 137).

Verapamil is also useful for the treatment of atrial fibrillation. Composite results from six series totaling 197 patients indicate that slowing of the ventricular rate occurred in 91% of patients, whereas conversion to sinus rhythm occurred in only 7% (119, 128-133). Once again the onset of action of intravenous verapamil is rapid. However, after an initial slowing, the ventricular rate begins to accelerate within 30 minutes of a bolus injection. Coexistent congestive heart failure accompanied by elevated sympathetic tone may blunt the beneficial slowing of the ventricular rate in atrial fibrillation of verapamil (138). Schamroth and colleagues (129) have reported a partial "regularization" of the ventricular rate in atrial fibrillation in 67% of patients treated with verapamil. This can be distinguished from the regularization due to emergence of a junctional rhythm in digitalis intoxication by the still discernible cycle-cycle variability.

In patients with atrial flutter, intravenous verapamil generally produces prompt reduction in ventricular rate by increasing atrioventricular block. Such a response was observed in 48% of 50 patients reported in five series (119, 129, 131-133). Conversion to sinus rhythm occurred in 32% of cases, while in another 18% the rhythm changed to atrial fibrillation. Singh and coworkers (126) have pointed out that the response to intravenous verapamil may serve as a useful diagnostic tool for differentiating atrial flutter from rapid paroxysmal supraventricular tachycardia. A sudden change in the rhythm would favor the diagnosis of paroxysmal supraventricular tachycardia, while increasing AV block would reveal flutter waves (126). Verapamil cannot be relied on for conversion from atrial flutter to sinus rhythm if the decision is made that prompt restoration of sinus rhythm is desirable (126).

A recent randomized double-blind trial comparing intravenous verapamil (0.075 to 0.15 mg/kg body weight) to placebo for control of paroxysmal supraventricular tachycardia and atrial flutter-fibrillation found verapamil to be highly effective. The incidence of conversion to sinus rhythm from paroxysmal supraventricular tachycardia and slowing of ventricular rate in atrial flutter-fibrillation was significantly higher in the verapamil-treated group (124).

The safety and effectiveness of administration of intravenous verapamil for supraventricular tachycardias in the setting of acute myocardial infarction were recently examined by Hagemeijer (139). Sixteen patients (eight with atrial fibrillation and eight with atrial flutter) were

treated with verapamil in doses ranging from 3 mg to 20 mg intravenously. The ventricular rate was slowed in all patients with atrial fibrillation, but none converted to sinus rhythm; seven of eight patients with atrial flutter converted to sinus rhythm, and in the remaining patient the ventricular rate was slowed. Two of 16 patients developed cardiogenic shock 5 and 7 hours after treatment of atrial flutter, and an additional patient died from recurrent infarction 36 hours after verapamil therapy. The reasons for the high rate of conversions of atrial flutter to sinus rhythm in this study compared with those cited earlier remain unexplained. The safety of verapamil therapy in patients with acute myocardial infarction needs further investigation.

VENTRICULAR ARRHYTHMIAS

The published experience with intravenous verapamil for control of ventricular arrhythmia is limited. Schamroth and colleagues (129) reported a decrease in the frequency of ventricular premature beats in 11 of 23 patients treated with verapamil and disappearance of ventricular ectopic activity in the remaining 12 patients. Heng and coworkers (119) were able to restore sinus rhythm in only one of five patients with ischemic heart disease and ventricular tachycardia; this conversion occurred only after the induction of significant hypotension. Another Ca^{++} channel blocking agent, perhexiline, has been used to treat chronic ventricular arrhythmias. Composite results from three studies indicate that in a maximum daily dose of 400 mg, perhexiline significantly reduced the frequency of ventricular premature beats in 28 of 37 patients, while paroxysms of ventricular tachycardia were eliminated in four cases (140-142). Vaughan Williams (143) has recently summarized the data on the antiarrhythmic properties of perhexilene and concluded that its clinical efficacy is probably a combined result of inhibition of the fast and slow inward currents and a reduction of myocardial oxygen consumption. Doses of nifedipine capable of lowering arterial pressure had no protective effect on the incidence of ventricular arrhythmias in patients during the early phase of myocardial infarction (144).

EFFECTIVENESS OF ORAL VERAPAMIL AS AN ANTIARRHYTHMIC AGENT

An important question regarding the clinical use of verapamil is its effectiveness when administered orally for control of ventricular rate in atrial fibrillation or prevention of atrial arrhythmias. Krikler (127) has summarized much of the uncontrolled data from European studies on these issues. Success in controlling atrial fibrillation, flutter, or tachycardia with doses as high as 720 mg/d (alone or in combination with quinidine) has been reported (133, 145-148). A trial of oral verapamil (240 to 480 mg/d) for recurrent atrial arrhythmias prevented recurrences in 24 of 32 patients (149). In a study of 23 digitalized patients with chronic atrial fibrillation, addition of verapamil (160 to 240 mg/d) reduced the resting heart rate from an average of 99 to 77 beats/min and peak heart rate in response to exercise from an average of 128 to 96 beats/minute (150). In another study suppression of nonparoxysmal junctional tachycardia occurred with 160 mg/d of verapamil during a 6-month period (160 mg/d) (151). Wellens and colleagues (152) followed-up five cases of paroxysmal supraventricular tachycardia in patients who were studied after intravenous verapamil (10 mg) and after 2 to 3 weeks of oral verapamil (80 mg three times daily) (152). The effects on intracardiac conduction and suppression of inducibility of tachycardia persisted after chronic oral verapamil administration but in some cases were of a smaller magnitude than after the intravenous dose. The differences between the clinical effectiveness of intravenous and oral verapamil may in part be explained by differences in tissue levels of the drug. The availability of methods to assay verapamil levels in biological fluids and tissues should help clarify the role of oral verapamil in the control of cardiac arrhythmias (153).

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APPENDIX 1

Calcium Channel Blocking Agents in the Treatment of Cardiovascular Disorders. Part II: Hemodynamic Effects and Clinical Applications

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The calcium channel blocking agents have multiple hemodynamic effects that make them potentially valuable in treating many cardiovascular disorders. They are potent dilators of coronary and peripheral arteries and in isolated tissue preparations exert potent negative inotropic, chronotropic, and dromotropic effects. In intact animals the peripheral arterial vasodilatation induces reflex-mediated adrenergic activity, which opposes the direct negative inotropic, chronotropic, dromotropic, and hypotensive effects. The individual calcium channel blockers have different relative potencies on various cardiovascular functions. The net hemodynamic and electrophysiologic effect of each agent, therefore, results from a complex interplay of direct and reflex phenomena. The clinical efficacy of these agents in classic angina pectoris relates to their ability to decrease afterload, myocardial contractility, and heart rate and increase coronary blood flow. The agents have been used to prevent coronary spasm in Prinzmetal's variant angina. The negative inotropic effects of verapamil are valuable in improving the symptoms and hemodynamic disturbances of hypertrophic cardiomyopathy. The role of these agents in treating arterial hypertension, unstable angina pectoris, acute myocardial infarction, and ischemia during cardiopulmonary bypass needs to be determined.

PART I of this review dealt with the manner in which calcium (Ca^{++}) channel blocking drugs affect the electrophysiologic properties of the heart and the manner in which these properties may be used in treating various arrhythmias. As was also discussed in Part I, Ca^{++} plays a pivotal role in the process by which electrical activation of the surface membrane of a cell leads to mechanical contraction. To aid in understanding the important hemodynamic effects of the Ca^{++} channel blocking agents we will review the excitation-contraction coupling process in heart muscle. Next we will discuss the effect of these agents on the coronary and systemic vascular beds and on the myocardium itself and how these properties of Ca^{++} channel blocking drugs can be used in treating various cardiovascular disorders.

Subcellular Basis for Excitation-Contraction Coupling

The classical studies of Ringer (154) carried out a century ago paved the way for the demonstration that Ca^{++} plays a critical role in coupling depolarization of the surface membrane to muscular contraction. In myocardial cells the contractile apparatus consists of the proteins actin and myosin, which slide past one another in an adenosine-triphosphate (ATP)-dependent process (155). The interaction between actin and myosin is inhibited by the regulatory proteins tropomyosin and troponin. With cellular depolarization the myoplasmic $[Ca^{++}]$ rises from 10^{-7} to 10^{-5} *M*. This increased Ca^{++} concentration permits the binding of Ca^{++} to troponin, which in turn releases troponin's inhibition of the contractile apparatus (156-158) and thereby allows muscular contraction to occur.

Although the quantity of transmembrane Ca^{++} influx during the action potential is too small to provide sufficient Ca^{++} to initiate contraction, it does trigger the release of intracellular stores of Ca^{++}, a process termed "Ca^{++}-triggered Ca^{++} release" (158). Thus, there are three potential mechanisms for increasing myoplasmic $[Ca^{++}]$: the slow inward Ca^{++} current, Na^{+}-Ca^{++} exchange across the sarcolemma, as previously discussed, and Ca^{++} release from the sarcoplasmic reticulum (158). Drugs with positive inotropic properties such as the β-adrenergic agonists act not only by augmenting the quantity of Ca^{++} influx through the slow channels of the surface membrane at the time of depolarization but also by enhancing the release of Ca^{++} from intracellular stores (for example, sarcoplasmic reticulum) and by increasing the sensitivity of the contractile system to Ca^{++} (159-161).

Contraction of vascular smooth muscle, such as that in the coronary arteries, also requires the interaction between actin and myosin. However, there are important differences between the biochemical process of contraction in vascular smooth muscle and that in myocardium (162) (Table 2). Although the regulatory protein tropomyosin is present in the contractile apparatus of vascular smooth muscle its function is unknown. The other protein that regulates contraction in myocardial cells, troponin, is replaced in vascular smooth muscle cells by a protein called calmodulin with a molecular weight of 16 500 daltons (162). When intracellular $[Ca^{++}]$ rises to 10^{-6} *M*, Ca^{++} binds to calmodulin, which then activates the enzyme myosin kinase. This enzyme phosphorylates the light chain of myosin, which then permits myosin to interact with actin, thereby leading to contraction of the smooth muscle cell and in turn vasoconstriction (163). It has been hypothesized that intracellular Ca^{++}, which is the trigger for contraction of vascular smooth muscle, is linked to the transmembrane Na^{+} gradient via the Na^{+}-Ca^{++} exchange mechanism discussed earlier. An increase in cytoplasmic Na^{+} may thereby lead to an influx of Ca^{++} sufficient to cause a sustained increase in vascular tone (164).

References 1 to 153, Table 1, and Figures 1 to 4 appear in Part I of this article, pp. 875-885

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In contrast to the effect on myocardial cells, an increase in the concentration of cyclic adenosine monophosphate (AMP) in vascular smooth muscle cells (for example, by β-adrenergic agonists) results in muscular relaxation (vasodilation). This occurs by two mechanisms: First, activation of cyclic AMP-dependent protein kinase enhances Ca^{++} uptake by membrane fractions, accelerates Ca^{++} efflux from smooth muscle cells, and prevents transmembrane influx of Ca^{++} (165). Second, myosin kinase, the enzyme that activates smooth muscle myosin mentioned above, can itself be inactivated by a separate cyclic AMP-mediated enzyme system (162, 166).

The specific mechanisms by which the calcium channel blocking agents may interfere with the excitation-contraction coupling process in myocardial or vascular smooth muscle cells include the slow inward Ca^{++} channel (1) and the transport of Ca^{++} among various intracellular compartments (65, 167, 168).

Hemodynamic Effects of Calcium Channel Blocking Agents

The Ca^{++} channel blocking agents exert different net effects in various types of tissue. In myocardium and in vascular smooth muscle from coronary, pulmonary, or cerebral arteries excitation-contraction coupling is preferentially inhibited while action potentials continue to occur (1, 169-171). Figure 5 illustrates that in the isolated guinea pig papillary muscle carefully chosen doses of verapamil may selectively reduce contractile force while the action potential upstroke velocity and the resting membrane potential remain unchanged. Of great clinical importance is the observation that the Ca^{++} channel blocking agents are three to 10 times more effective in inhibiting contraction in coronary artery smooth muscle than in myocardial contractile cells (1, 172). This differential effect permits Ca^{++} channel blockers to dilate the coronary arteries in doses that do not decrease myocardial contractility (73, 173).

The Ca^{++} channel blocking agents can influence cardiovascular hemodynamics by their three principal actions: coronary arterial dilatation, peripheral arterial dilatation, and a negative inotropic effect. The net hemodynamic effects of these agents vary depending on the relative strength of each individual action. Because the dose response curves for each drug vary for each of these three actions the dose of the agent used will determine the relative contribution of each action to the net hemodynamic effect. In addition, these direct hemodynamic actions of the Ca^{++} channel blocking agents may evoke reflex mechanisms that contribute to, or may even be the principal determinant of, the net hemodynamic effect.

Table 2. Comparison of Myocardial and Vascular Smooth Muscle Contractile Systems

	Myocardial Cells	Smooth Muscle Cells
Principal contractile proteins	Actin Myosin	Actin Myosin*
Regulatory proteins	Tropomysin Troponin	Calmodulin
Effect of ↑ $[Ca^{++}]_i$↑	↑Contraction	↑Contraction (vasoconstriction)
Effect of ↑ cellular cyclic AMP	↑Contraction	↓Contraction (vasodilatation)

* Requires phosphorylation of light chain to initiate interaction with actin.
† $[Ca^{++}]_i$ = intracellular calcium ion concentration.

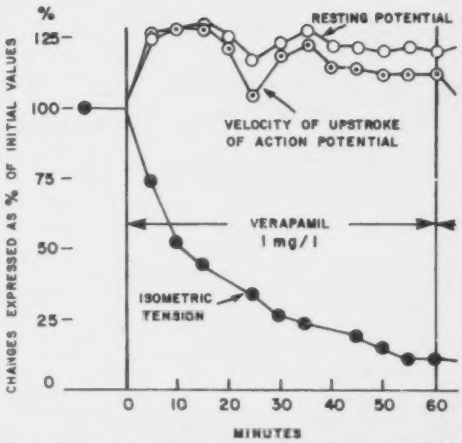

Figure 5. Uncoupling of the excitation-contraction process. Calcium-ion-dependent contractile force of a guinea pig papillary muscle is selectively reduced by verapamil, 1 mg/L, whereas the action potential upstroke velocity and resting membrane potential are unchanged. (From Reference 357; used with permission.)

EFFECTS ON THE CORONARY CIRCULATION

Each of the Ca^{++} channel blockers decreases smooth muscle tone in the coronary arteries, thereby reducing coronary vascular resistance and increasing coronary blood flow (1). The latter has been demonstrated by direct measurement with electromagnetic flowmeters (74, 173, 174) by measurement of coronary sinus flow (73, 172, 175), and by measurement of coronary sinus oxygen content (173, 176-178). The degree of coronary vasodilatation has been measured in vitro by evaluating the reactivity of coronary artery muscle strips. Figure 6 illustrates the relative potency of each of the Ca^{++} channel blocking agents in reducing K^+-induced contractures of pig coronary artery strips. In equimolar doses, nifedipine proved to be the most potent coronary vasodilator, being several thousand times more potent than papaverine, the standard reference for agents that produce smooth muscle relaxation.

The Ca^{++} channel blocking agents were initially thought to be competitive β-adrenergic blocking agents because they appeared to antagonize cardiac adrenergic effects (179). Subsequent experience, however, has demonstrated that these agents decreased the vascular responsiveness to stimulants of the α-adrenergic, β-adrenergic, and angiotension receptors in the dog (180). Cardiac glycoside-induced coronary vasoconstriction is also blocked by Ca^{++} channel blockers (181, 182). Contrac-

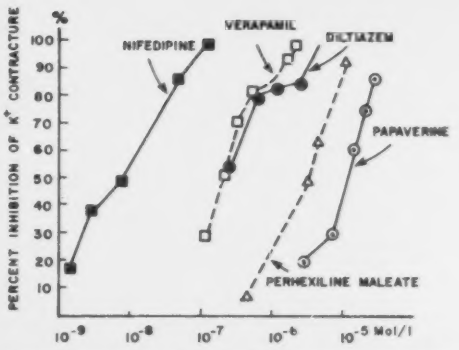

Figure 6. Suppression of K^+-induced contractures in pig coronary strips caused by different Ca^{++} channel blocking agents. The strips were brought into contracture by depolarization in Tyrode's solution rich in K^+ (43 mM of potassium chloride, exposure 40 minutes per experiment). Subsequently the Ca^{++} channel blockers were added in various concentrations. The degree of relaxation thus achieved is expressed as the percentage of the maximal peak tension reached shortly before the addition of the Ca^{++} channel blockers. Throughout the experiments the test bath was oxygenated with a gas mixture of 97% oxygen and 3% carbon dioxide at 35 °C, pH 7.4. Isometric tension was recorded continuously using a mechanoelectronic transducer. (From Reference 380; adapted with permission.)

tion of normally quiescent arterial smooth muscle can be induced experimentally by the addition of tetraethylammonium, which provokes spontaneous Ca^{++} dependent action potentials. Verapamil (10^{-5} *M*) has been shown to inhibit such activity in preparations of large and small canine coronary arteries (183). The relaxant effect of Ca^{++} channel blockers on smooth muscle is therefore due to inhibition of Ca^{++} influx, a critical step in the excitation-contraction process that is not dependent on the receptor type responsible for stimulation. The vasodilating effect of these drugs can be blunted or abolished only by increasing the extracellular [Ca^{++}] (184), and it is unaffected by β-adrenergic blockade, catecholamine depletion, or vagotomy (185-187).

The Ca^{++} channel blocking agents also increase flow through coronary collateral vessels. Experimental studies have shown that diltiazem (188), nifedipine (189-191), or verapamil (192) administered soon after coronary artery ligation augment flow distal to the ligature, as ascertained by direct measurement of retrograde coronary flow (191, 192), by the tracer microsphere technique (188, 191), or by plastic casts made of the coronary vasculature (189). This enhanced collateral flow to the ischemic area may be due to a drug-induced reduction in coronary arteriolar resistance in vessels supplying collaterals to the ischemic zone or in vessels in the ischemic zone distal to the ligature (191).

EFFECTS ON THE PERIPHERAL CIRCULATION

The vasodilating effects of the Ca^{++} channel blockers are not confined to the coronary circulation. Similar to the effects observed in coronary arteries, tetraethylammonium-induced Ca^{++}-dependent action potentials in superior mesenteric artery strips from guinea pigs are inhibited by verapamil (193). In the anesthetized animal Ca^{++} channel blocking agents dilate the pulmonary artery (170), hindlimb (180), and the hepatic (194), femoral (172, 194), renal (172, 195), and superior mesenteric vascular beds (185, 194). Nifedipine dilates the renal arteries, abolishing autoregulation in the experimental animal (172), and at least in humans, it also dilates the cerebral arteries (196). This widespread vasodilation reduces systemic vascular resistance both in animals (172, 173, 176, 180, 184-186, 197-201) and in humans (178, 202-209). Comparative studies in dogs on the vasodilatory effect of nifedipine, verapamil, and perhexiline show that the increase in blood flow is greatest in the femoral arterial bed followed closely by the coronary, renal, and the mesenteric beds (73, 210). Diltiazem was found preferentially to dilate the coronary bed; at a dose that doubles coronary blood flow (0.1 mg/kg of body weight), diltiazem produced only 25%, 37%, and 10% increases in femoral, carotid, and renal blood flows, respectively (187).

COMPARISON OF THE HEMODYNAMIC EFFECTS OF CALCIUM CHANNEL BLOCKING AGENTS WITH NITRATES

The vascular effects of Ca^{++} channel blocking agents are similar, but not identical, to those of nitroglycerin and other organic nitrates. Nitroglycerin and related compounds have been shown to block Ca^{++}-dependent excitation-contraction coupling of vascular smooth muscle, even though these drugs have no corresponding action on the myocardium (211). Some of the major differences between the nitrates and the Ca^{++} channel blockers can be demonstrated using K^+-depolarized coronary artery strips (1). The onset of nitrate-induced relaxation is much more rapid that that observed with Ca^{++} channel blockers, and the relaxation is always incomplete; even at high nitrate concentrations a residual contracture of 20% to 40% remains. Unlike the effect of the Ca^{++} channel blockers, nitrate-induced relaxation is transient in most cases so that coronary vascular tone tends to recover even in the presence of nitrates. Addition of Ca^{++} to the preparation instantaneously neutralizes the effect of the nitrates.

In patients with ischemic heart disease Lichtlen and colleagues (212) detected major differences in effects on coronary vessels among various antianginal drugs. Myocardial blood flow was assessed with the radioactive xenon technique, and sequential left ventriculograms were used to assess regional wall motion. Nitroglycerin decreased mean aortic pressure and global myocardial flow, as well as regional flow both to normally perfused areas and to poststenotic, underperfused areas. Nevertheless, left ventricular wall motion improved, and ventricular volumes decreased. The improvement of ventricular function resulted from the decreased preload produced by extracardiac vasodilatation in combination with a reduced afterload. In contrast, nifedipine consistently increased global flow and regional flow both to normal and poststenotic, underperfused areas in spite of a decrease in mean aortic pressure, reflecting primary coronary vasodi-

Table 3. Relative Effects of Calcium Channel Blocking Agents on Various Cardiovascular Functions*

	Nifedipine	Verapamil	Diltiazem	Perhexiline
Negative chronotropic action	1	1	1/3	(1/30)
Negative inotropic action	1	1/13	1/40	(1/100)
Negative dromotropic action	1	1/2	1/2	(1/100)
Vasodilator action	1	1/12	1/26	(1/36)

* Ascertained from the addition of equimolar doses of the different Ca^{++} channel blocking agents to isolated tissue preparations. (From Reference 73; used with permission.)

lation. Although mean aortic pressure was decreased by both nitroglycerin and nifedipine, only nifedipine caused a concomitant increase in coronary blood flow (212). After nifedipine administration there were no consistent changes in left ventricular volume or regional wall motion. Beta-adrenergic blockers reduced regional flow and contractility in both normal and underperfused areas.

The nitrates and Ca^{++} channel blockers also differ in their effects on the arterial resistance and the venous capacitance beds. In both experimental animals (172, 197, 199) and humans (213-215) the primary peripheral effect of the Ca^{++} channel blockers is to decrease arterial resistance, and although the issue has not been entirely settled (176, 216), most investigators agree that the Ca^{++} channel blocking agents have little or no effect on venous capacitance. On the other hand, the nitrates cause dilatation, especially of the venous capacitance vessels (197, 199, 200, 213, 215) and exert a lesser effect on the arterial resistance vessels. The Ca^{++} channel blockers therefore can be considered to exert their major peripheral effect on afterload, whereas the nitrates affect both preload and afterload.

EFFECTS ON MYOCARDIAL CONTRACTILITY

The net effect of the Ca^{++} channel blocking agents on myocardial contractility is a complex composite of direct and reflex-mediated phenomena. In-vitro experiments, in which reflex activity does not occur, show that all Ca^{++} channel blocking agents exert a clear dose-dependent inhibition of contractility that can be reversed by increasing the extracellular Ca^{++} concentration (73, 171, 172, 176, 201, 217). As illustrated in Table 3, comparative studies indicate that the relative potency (on a weight basis) of direct negative inotropic effect of the Ca^{++} channel blockers is in descending order: nifedipine, verapamil, diltiazem, and perhexiline (57, 73, 74). Associated with this negative inotropic effect is a dose-dependent decrease in myocardial oxygen consumption (176). In the conscious animal, or in animals anesthetized with opiates alone (in which reflex mechanisms are relatively well preserved), low doses of the Ca^{++} channel blocking agents may produce a slight negative inotropic effect (176). However, higher doses produce greater peripheral arterial vasodilatation, and the direct negative inotropic effect is offset by the baroreceptor-mediated reflex positive inotropic response and tachycardia (176, 218). Net myocardial oxygen consumption remains decreased in spite of these reflex mechanisms, however, because the decrease in oxygen demand from reduced afterload exceeds the increase in oxygen demand caused by the reflex-mediated positive inotropic response and tachycardia (172-176). It has also been shown that low doses of the Ca^{++} channel blocking agents, which produce vasodilation, may be insufficient to produce a negative inotropic effect (74). The latter may therefore be insignificant in doses used clinically. For example, using an experimental model that incorporates both an intact, anesthetized dog and an isolated papillary muscle preparation in series, Hashimoto and associates (210) demonstrated that a dose of nifedipine that doubled coronary flow in the former (0.3 to 3 μg/kg of body weight) was not associated with a direct negative inotropic effect in the latter. Only much higher doses of nifedipine ($\geq$ 10 μg/kg), which were accompanied by marked hypotension in the intact dog, produced a negative inotropic effect on the isolated papillary muscle.

COMPARATIVE HEMODYNAMIC EFFECTS

Table 3 illustrates the relative net potencies of the Ca^{++} channel blocking agents on various cardiovascular functions when administered in equal doses by weight to isolated tissue preparations (73, 219). Nifedipine is the most potent agent in all of its actions and perhexiline the least potent, whereas verapamil and diltiazem are intermediate. The significance of these differences is apparent when examining the net effects of these agents. Because nifedipine is a potent vasodilator it elicits a strong reflex β-adrenergic response. This in turn counterbalances its negative inotropic, chronotropic, and dromotropic effects (69, 176, 218). The net effect of nifedipine, therefore, is that of relatively pure vasodilatation with little resultant electrophysiologic or inotropic effect. In contrast, doses of verapamil that exert the same degree of vasodilatation as does nifedipine produce greater negative dromotropic effects (69), and reflex induced β-adrenergic activity may not completely offset these direct electrophysiologic effects. When given in equipotent doses to double coronary blood flow in barbiturate-anesthetized dogs, verapamil (100 μg/kg of body weight) and diltiazem (100 μg/kg) caused a prolongation of atrioventricular (AV) conduction time and a prolongation of the functional refractory period of the AV node; nifedipine (3 μg/kg) had no significant effect on these variables (84). Therefore, the administration of verapamil or diltiazem as coronary vasodilators may be accompanied by AV nodal conduction disturbances. Conversely, however, verapamil can be used in low doses for its antiarrhythmic effects, particularly on the AV node, with little hemodynamic consequence (125).

Walsh and coworkers (220) compared the hemodynamic effects of equimolar clinical doses (0.04 to 0.17

Table 4. Clinical Pharmacology of Calcium Channel Blocking Agents

Drug	Dose	Absorption	Onset of Action	Peak Effect	Plasma Half-Life	Protein Binding
						%
nifedipine	10–20 mg/4–8 h sublingually or orally	>90% sublingually and orally	<1 min intravenously <3 min sublingually <20 min orally	1–2 h orally	4 h	90
verapamil	75–150 μg/kg intravenously 80–160 mg/8 h orally	>90% orally	<2 min intravenously 2 hrs orally	10–15 min intravenously 5 h orally	3 to 7 h	90
diltiazem	75–150 μg/kg intravenously 60–90 mg/8 h orally	>90% orally	<15 min orally	30 min orally	4 h	80
perhexiline	100–200 mg/12 h orally	>90% orally	<1 hour orally	12 h orally	3–12 d	>90

mg/kg intravenously) of verapamil and diltiazem on left ventricular performance in conscious dogs. Despite equal changes in heart rate and aortic pressure, verapamil, but not diltiazem, decreased left ventricular function. The negative inotropic effects of verapamil can also be potentiated by concurrent administration of β-adrenergic blocking agents (221), but no negative inotropic effect is produced by diltiazem even after full beta blockade with propranolol (2 mg/kg) (220).

NET HEMODYNAMIC EFFECTS AT REST

In humans the direct and net effects of Ca^{++} channel blockers can be demonstrated by intracoronary artery and systemic administration, respectively. Selective administration of nifedipine into a coronary artery reveals two of the direct effects: coronary vasodilatation and negative inotropism. Accordingly, administration of 0.1 mg of nifedipine into the left coronary artery produces an increased coronary sinus oxygen saturation (178), increased left ventricular end-diastolic pressure, decreased left ventricular pressure, left ventricular stroke work (dP/dt), maximum velocity (Vmax), and "T," a diastolic relaxation constant derived from the rate of left ventricular pressure decline after peak negative dP/dt (222, 223). In contrast, the intravenous administration of doses of nifedipine that increase coronary sinus oxygen saturation to a similar degree demonstrates both direct as well as reflex hemodynamic events. Only a reduction in left ventricular systolic pressure occurs, a consequence of the peripheral arterial vasodilatation; all the negative inotropic effects are counterbalanced by reflex mechanisms (223).

As in experimental animals, systemic administration of nifedipine in humans leads to reduction of total peripheral and coronary vascular resistances with an accompanying increase in coronary flow (224). The effect of a single systemic dose of nifedipine on left ventricular dP/dt in man is variable, reflecting the interplay between direct and reflex events. After 10 mg of nifedipine is given sublingually, dP/dt drops slightly. After a 20-mg dose, however, with the reflex β-adrenergic stimulation elicited from the decrease in peripheral vascular resistance, left ventricular dP/dt increases slightly (224).

The net hemodynamic results with verapamil have been somewhat more variable. Some investigators note a predominant reduction in peripheral arterial resistance with a reflex tachycardia (209), similar to the effects of nifedipine, whereas others have observed that although blood pressure generally decreases, the reflex tachycardia may be blunted by the more prominent direct negative chronotropic effect (205-207, 225-229). These inconsistencies are not due to different doses of verapamil but may be related to the fact that small numbers of patients were used and that the severity of underlying cardiac disease was different.

The Ca^{++} channel blocking agents have a variable effect on left ventricular end-diastolic pressure in humans. Although venous return is minimally affected, if at all, by these agents, left ventricular end-diastolic pressure at rest may fall after their administration because of the reflex augmentation of contractility and heart rate referred to above. On the other hand, if the direct negative inotropic effects are not counterbalanced by reflex events, then left ventricular end-diastolic pressure rises. Accordingly, because verapamil induces less arterial hypotension than nifedipine and therefore provokes less reflex β-adrenergic activity, left ventricular end-diastolic pressure generally rises after its administration (201, 206, 207). Nifedipine exerts a more variable effect on left ventricular end-diastolic pressure, partly because of its more prominent vasodilatory effects. Various investigators have found that after administration of nifedipine it increases (202, 204), decreases (176-178, 203, 204, 230), or does not change (230).

NET HEMODYNAMIC EFFECTS DURING EXERCISE

The hemodynamic response to exercise after systemic administration of nifedipine to patients with coronary artery disease is similar to that seen in the resting state.

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Table 4. (Continued)

Metabolism and Elimination	Side Effects	Indications	Drug
Extensively metabolized to inert products 80% excreted via kidney	Headache, hypotension, flushing, digital dysesthesias, leg edema	Variant angina, classic angina, ? unstable angina, ? acute myocardial infarction, ? arterial hypertension, ? cardiopulmonary bypass	nifedipine
Extensively metabolized in liver 85% first pass hepatic elimination after oral administration 75% excreted via kidney	Constipation, headache, vertigo, hypotension, atrioventricular conduction disturbances	Re-entrant supraventricular tachycardia and other supraventricular tachycardia, variant angina, classic angina, ? idiopathic hypertrophic subaortic stenosis	verapamil
Extensively metabolized 60% excreted via liver 35% excreted via kidney	Headache, dizziness, flushing, atrioventricular conduction disturbances	Variant angina	diltiazem
Extensively metabolized 40% excreted via liver 60% excreted via kidney	Elevation of liver enzymes, accentuation of abnormal glucose metabolism, peripheral neuropathy	Classic angina	perhexiline

There is a dose-dependent reduction of mean arterial pressure, left ventricular systolic pressure, and total peripheral resistance with a reflex increase in heart rate, stroke volume, cardiac index, and left ventricular dP/dt (231-233). The augmented coronary flow observed at rest, however, is markedly less or completely absent with exercise (231). Although the left ventricular end-diastolic pressure increases with exercise in patients with coronary artery disease after nifedipine is given, the increase from resting levels is less than that observed during the control exercise (231, 234).

Because diltiazem and perhexiline exert relatively more prominent negative chronotropic effects than vasodilatory effects, these agents often produce an actual reduction in heart rate and no change or only a variable decrease in blood pressure (214, 225, 235-241).

In summary, the hemodynamic effects of the Ca^{++} channel blocking agents result from a complex interplay of direct and reflex effects. Nifedipine increases myocardial oxygen supply by coronary vasodilatation and decreases myocardial oxygen demands by decreasing afterload. Verapamil, diltiazem, and perhexiline exert similar effects in augmenting oxygen supply and also may lower oxygen demand by decreasing heart rate and reducing afterload.

Clinical Pharmacology and Indications For Use of Calcium Channel Blocking Agents

NIFEDIPINE

Pharmacokinetics: After oral or buccal administration of nifedipine, 90% of the administered drug is absorbed (242, 243) (Table 4). The drug is detectable in the serum 3 minutes after buccal and 20 minutes after oral administration, and peak blood concentration occurs 1 to 2 hours after oral use. More than 90% of the circulating drug is protein bound; it is completely metabolized to inert products. Approximately 75% of the metabolized drug is eliminated via the kidney and up to 15% through the gastrointestinal tract. The plasma half-life is 4 to 5 hours. Nifedipine does not appear to interact with other drugs and may be safely administered together with nitrates, beta blockers, digoxin, furosemide, anticoagulants, antihypertensive and antidiabetic agents (224).

Side Effects: Nifedipine frequently produces mild side effects, which generally result from its vasodilatory effects (224). Headache occurs in about 5% of patients on chronic therapy; hypotension, digital dysesthesias, flushing, dizziness, nausea and vomiting, tiredness, sedation, or leg edema occur less frequently. Treatment was discontinued because of intolerable side effects in only 4.7% of 5008 patients on chronic therapy (224).

A small fraction of patients develop an exacerbation of ischemic symptoms after nifedipine administration (244-246). Nifedipine possibly could exert a detrimental effect by imbalancing myocardial oxygen supply and demand by causing severe hypotension in the face of severe fixed obstruction or by producing a coronary steal. Nifedipine causes no alteration in pulmonary, hepatic, or renal function, and it does not affect the hematopoietic system (224).

Indications and Dose: As described below, nifedipine is extremely useful for the prevention of coronary artery spasm in patients with variant angina and is also of value in the therapy of classic exertional angina. Unlike the other Ca^{++} channel blockers it can be added to beta-blocker therapy with relative safety to provide additional therapeutic benefit. Nifedipine may also be of value in the therapy of unstable angina, acute myocardial infarction, and hypertension, but definitive recommendations must await the results of ongoing randomized studies. It may also be valuable in protecting myocardium that becomes ischemic during the course of open-heart operations. Nifedipine has not proved as useful as verapamil in the treatment of supraventricular tachyarrhythmias.

The useful starting dose of nifedipine is 10 mg three times a day. The dose should be increased until symptoms are relieved or undesirable side effects occur. The maximal dose generally recommended is 120 mg daily.

Administering the drug every 4 hours may be necessary if symptoms recur less than 6 to 8 hours after a dose.

VERAPAMIL

Pharmacokinetics: Verapamil is well absorbed after oral administration. Measurable electrophysiologic effects appear at 2 hours and peak at 5 hours after a single dose (125, 247). A verapamil delayed release preparation has been reported to have an onset of action of 6 hours and a duration of action of 14 hours (247). After intravenous administration the hypotensive effect is short-lived: The peak effect occurs at 5 minutes, and by 10 to 20 minutes the effect is dissipated (207, 248). The negative dromotropic effect, on the other hand, is more sustained after intravenous administration: The onset of action is within 1 to 2 minutes, the peak effect occurs at 10 to 15 minutes, and an effect is still detectable after 6 hours. Preferential uptake and binding of verapamil by the AV nodal tissues has been suggested because the duration of the depressant effect on the AV node considerably outlasts the duration of the drug's hemodynamic actions (125). The drug exhibits a biexponential decline after both intravenous and oral administrations, with an initial distribution phase lasting from 18 to 35 minutes and a much slower elimination phase with a half-life varying from 3 to 7 hours (249). Up to 70% of an oral or intravenous dose is excreted by the kidney, and 15% is eliminated via the gastrointestinal tract. Despite almost complete gastrointestinal absorption, the overall bioavailability after oral administration ranges from 10% to 20%, indicating substantial first-pass metabolism in the liver. This hepatic degradation of verapamil accounts for the marked differences between the oral and intravenous doses needed to obtain a similar physiologic effect (249). The oral dose must be at least eight to 10 times larger than the intravenous dose to achieve comparable plasma verapamil levels.

Ninety percent of the verapamil in the serum is bound to protein (249). Plasma levels of the metabolites of verapamil may be at least twice as high as those of the parent drug itself (249). These metabolites need further study because they may contribute to the overall pharmacologic and therapeutic actions of verapamil.

Side Effects: Adverse effects of oral and intravenous verapamil occur in approximately 10% of patients, but they are severe enough to require discontinuation of the drug in only 1% of patients (125). Oral verapamil is extremely well tolerated with a very low prevalence of gastric intolerance and constipation, vertigo, headache, and nervousness. Intravenous administration of verapamil occasionally produces side effects resulting from an excess of the pharmacologic actions of the drug, including hypotension and disturbances of AV conduction (250, 251). Serious side effects of intravenous verapamil such as hypotension, bradycardia, and occasionally even ventricular asystole have been reported, although most of these have occurred in patients receiving concomitant β-adrenergic blockade (252-254) or in patients who have severe hypertrophic cardiomyopathy (255).

Indications and Doses: Verapamil is used primarily for its ability to block conduction through the AV node and is most efficacious for the termination and the prevention of paroxysmal supraventricular tachycardia. It is moderately useful for rate control as an adjunct to digitalis glycosides in patients with atrial fibrillation or flutter or for conversion of these arrhythmias to normal sinus rhythm. It has a minimal effect on the accessory pathway in preexcitation syndromes and hence is effective in interrupting a tachycardia in that syndrome only when the re-entrant circuit involves the AV node. Verapamil may be as effective as nifedipine for the primary therapy of classic angina pectoris, but because β-adrenergic blockers and verapamil independently exert negative inotropic, chronotropic, and dromotropic effects, the agents should not be used together, particularly in patients with depressed left ventricular function or abnormalities of impulse generation or conduction. Verapamil may also be a valuable agent for the treatment of hypertrophic cardiomyopathy, as described below.

The main contraindications to the use of verapamil are the presence of hypotension, severe left ventricular dysfunction, atrioventricular block, and sinus node dysfunction (115, 125).

For the termination of atrial arrhythmias, the most commonly used dose is an injection of 10 mg (or 0.15 mg/kg body weight) of verapamil administered over a 60-second period with electrocardiographic and blood pressure monitoring (125, 248). If the injection does not terminate the arrhythmia or cause untoward effects, a similar dose may be administered 30 minutes later. If a continuous effect is needed, an infusion of verapamil, 0.005 mg/kg · min, can be administered. The dose should be reduced in patients with myocardial dysfunction. The usual starting dose of verapamil for oral administration is 40 to 80 mg every 8 hours. The dose may then be increased rapidly over the next 2 or 3 days to the usual dose of 240 to 360 mg daily. Some authors have suggested that doses as high as 720 mg daily may be used in patients without known contraindications (125).

DILTIAZEM

Pharmacokinetics: Diltiazem is absorbed rapidly and almost completely after oral administration; it first appears in the plasma 15 minutes after oral administration, and peak concentrations occur after 30 minutes (256, 257). The plasma half-life is approximately 4 hours. Approximately 80% of the drug is bound to plasma proteins; about 60% of the drug is metabolized by the liver, and the remainder is excreted by the kidneys.

Side Effects: Although there is relatively little experience with the drug, adverse effects appear to be infrequent. Atrioventricular nodal conduction disturbances may accompany intravenous administration (258). Drug rash, dizziness, headaches, flushing, and gastrointestinal discomfort have been reported in some patients (259). One study has suggested that diltiazem exerts a direct inhibitory action on the renal tubular resorption of sodium (260).

Indications and Dose: Diltiazem appears to be effective for the therapy of variant angina (261-264), but there is

very little information on its role in classical angina, hypertension, or arrhythmias. The safety of concurrent administration of β-adrenergic blocking agents with diltiazem has yet to be established. The usual oral dose is 30 to 60 mg every 8 hours.

PERHEXILINE

Pharmacokinetics: Although the pharmacokinetics of perhexiline have not been studied extensively, absorption appears to be rapid and almost complete after an oral dose. Maximum blood levels are attained in 1 hour, and detectable levels are present for about 7 hours (265-267). Perhexiline is 90% bound to plasma protein. It is extensively metabolized by the liver, primarily by hydroxylation (268), and about 40% of the metabolites are excreted by the fecal route and 60% by the kidney.

Side Effects: The adverse effects of perhexiline have been recently reviewed (143). The commonest adverse effect is mild elevation of serum enzymes, particularly serum glutamic-oxalacetic and glutamic-pyruvic transaminases (SGOT, SGPT), alkaline phosphatase, and lactic acid dehydrogenase as a consequence of hepatic dysfunction (269, 270). These elevations are usually reversible after discontinuation of the drug.

Dose-dependent diuresis, natriuresis, and chloruresis have been observed during perhexiline treatment (271), associated with a slight weight loss and decrease in creatinine clearance. Whether this phenomenon reflects actual renal damage or an alteration in renal hemodynamics is unknown. Perhexiline also accentuates the delayed and increased insulin secretion after an oral glucose tolerance test in diabetic patients with coronary artery disease (9). A symmetrical, proximal, sensorimotor neuropathy with reduced nerve conduction velocity has been noted to occur in some patients after prolonged perhexiline use (268, 272). The patients who develop neuropathy during perhexiline treatment may be those who metabolize the drug more slowly and therefore accumulate higher plasma concentrations of the parent compound (268). The neuropathy regresses after cessation of perhexiline therapy, although complete recovery may be quite delayed.

Indications and Dose: Perhexiline is efficacious for the treatment of classical angina although its desirability as a primary agent may be limited by its side effects and the availability of other better tolerated agents. It may have a role in the therapy of variant angina, hypertension, or rhythm disturbances, but further studies in these conditions are needed. The usual starting dose of perhexiline is 100 mg twice a day, and the average maintenance dose is 150 to 200 mg twice a day.

Clinical Applications

VARIANT ANGINA

In recent years it has been documented that coronary artery spasm is the pathogenetic mechanism of "variant angina," the syndrome in which patients develop spontaneous episodes of chest pain associated with reversible ST-segment elevation. The presence of coronary vasospasm has been confirmed in these patients by direct angiographic visualization (273-276) and by thallium scintigraphy (277). Hemodynamic monitoring has demonstrated that pain and evidence of ischemia precede any increase in the major determinants of myocardial oxygen demand (278), further implicating a primary reduction in oxygen supply as the cause of transient myocardial ischemia. Because the Ca^{++} blockers are extremely potent coronary vasodilators, there has been great interest in treating variant angina with these agents.

Nifedipine, verapamil, diltiazem, and perhexiline have all been used in the treatment of variant angina, with generally excellent results. Initial reports from Japan (279, 280) and the United States (281) indicated that nifedipine, 40 to 80 mg daily, dramatically reduced symptoms in patients with variant angina. Experience in the United States with the use of nifedipine in 127 patients with coronary spasm, most of whom had previously been treated with conventional antianginal therapy with inadequate results, has recently been summarized (282). The drug eliminated spontaneous attacks of pain and ST-segment elevation in 63% of the patients; in 87% of the patients the frequency of attacks decreased by at least 50%. Malignant ventricular arrhythmias and conduction disturbances associated with episodes of variant angina were also prevented by nifedipine, presumably through elimination of the ischemia that was responsible for the electrical instability (282-285). This remarkable benefit from nifedipine occurred irrespective of the presence of underlying fixed obstructive coronary disease. The daily dose ranged from 40 mg to 160 mg. In only 7% of cases was nifedipine treatment terminated because it was considered ineffective in controlling anginal attacks. Side effects from nifedipine occurred in 39% of the patients, but were severe enough to require withdrawal of the drug in only 5%. Nifedipine also has been shown to block consistently the coronary spasm provoked by ergonovine in patients with variant angina (286, 287).

Experience in treating this syndrome with verapamil has also been quite encouraging. Freedman and colleagues (288) reported on 17 patients with variant angina, some of whom had failed to respond to treatment with beta blockers. Verapamil was administered in a dosage of 120 to 320 mg daily for 8 months. Fifty-nine percent of the patients became entirely asymptomatic, and an additional 29% noted a reduction in their episodes of pain to less than two attacks per month. Severi and associates (289) recently reported the long-term follow-up (1 to 8 years) of 138 patients with spontaneous angina and ST segment elevation who were treated with verapamil, long-acting nitrates, or both. By 1 year 20%, and by 4 years, 50% of the patients were asymptomatic. Remission was more likely in patients with less severe underlying coronary artery disease.

There is less experience with the use of the other Ca^{++} channel blockers for the treatment of variant angina. A double-blind crossover study of diltiazem treatment for 2 weeks in seven patients with variant angina showed that 240 mg daily produced an 89% reduction in the number of episodes of pain and in the number of nitroglycerin tablets consumed (261). In two small studies carried out on a total of nine patients diltiazem prevented drug-in-

duced or exercise-induced coronary spasm (262, 263). Mizgala and colleagues (290) reported results in 33 patients with variant angina who were treated with perhexiline, 300 to 1000 mg daily. Although 75% of the patients became asymptomatic within 5 days, only 48% remained asymptomatic after 11 months of therapy. Adverse effects limited the use of perhexiline in 24% of patients. Perhexiline, 200 to 400 mg daily, prevented episodes of variant angina in three patients (291), although in another series of 10 patients with variant angina (287) perhexiline, 400 mg twice a day, did not suppress episodes of variant angina nor diminish the positive response to ergonovine challenge.

There are few studies that directly compare the efficacy of the various Ca^{++} channel blocking agents for the treatment of variant angina. A Japanese Multicenter Study of 286 patients showed that either nifedipine or diltiazem completely eliminated evidence of ischemic episodes in approximately 75% of the patients and that clinical improvement occurred in more than 90% of the patients treated with these agents (264). Verapamil was significantly less effective, eliminating variant angina in only 11% of cases. Waters and coworkers (286) evaluated the ability of the Ca^{++} channel blockers to prevent the coronary vasospastic response to a progressive ergonovine challenge. Although nifedipine, diltiazem, and verapamil consistently increased the threshold for ergonovine to produce spasm, nifedipine was most efficacious in preventing coronary spasm. Finally, the combination of a long-acting nitrate and a Ca^{++} channel blocking agent may be more effective than either agent alone in preventing attacks of variant angina (281, 292). Withdrawal of nitrate preparations from patients with variant angina should be done with caution (281).

CLASSIC ANGINA PECTORIS

The Ca^{++} channel blocking agents have also been shown to be effective in the treatment of classic angina pectoris. Their beneficial effect may occur through several possible mechanisms. By decreasing peripheral vascular resistance or afterload and reducing myocardial contractility the agents may decrease myocardial oxygen consumption and thereby improve the relation between myocardial oxygen supply and demand, although reflex β-adrenergic stimulation may oppose these direct effects. Finally, inappropriate coronary vasoconstriction may contribute to the production of myocardial ischemia in patients with classic angina (293, 294). Nifedipine has been shown to abolish this inappropriate coronary vasoconstriction, thus indicating another mechanism by which the Ca^{++} channel blocking agents may be effective in the therapy of classic angina (294).

Efficacy of the Agents as Primary Therapy: Nifedipine has been extensively studied in the treatment of classic angina. In randomized, double-blind studies using a single sublingual dose of 10 or 20 mg, patients experienced a 23% to 100% reduction in the development of angina and were able to increase their exercise tolerance by 20% to 70% on a graduated stress test over what they could do when taking placebo (224, 295-298). Four double-blind controlled studies using a single dose of nifedipine showed an average reduction of 32% in exercise-induced ischemic ST-segment depression (299-301). Similar beneficial results have been shown in studies of chronic nifedipine therapy in over 4000 patients treated for periods ranging from 2 weeks to 3 years (224, 302). Tachyphylaxis to the hemodynamic effects of nifedipine has not appeared in experimental animals (189) or in humans (303). Becker and coworkers (303) found that exercise-induced ST segment depression was reduced by 48% 30 minutes after a single sublingual nifedipine dose of 20 mg. This improvement in exercise-induced ischemic ST depression persisted when therapy with 20 mg of nifedipine three times a day was continued for 6 weeks. One week after the drug was discontinued, however, the amount of ST depression produced by exercise returned to pretreatment levels. The dosages used in these studies ranged from 10 to 60 mg daily. Although the value of higher doses of nifedipine in exertional angina is yet to be ascertained, it is suggested that the improvement in angina is dose dependent (288, 304) and that doses of 120 mg/d or more may be needed and are relatively well tolerated.

The beneficial antianginal effect was accompanied by dose-dependent reductions in peripheral vascular resistance and systemic arterial pressure. The rate pressure index, or double product, an index of myocardial oxygen demand, was decreased at any given workload (297, 299, 305). The double product at the onset of angina or termination of the exercise, however, was similar for control and nifedipine-treated periods, indicating that the improved exercise capacity was due to reduced oxygen demand rather than augmented myocardial oxygen supply (302). The enhanced exercise ability in patients taking nifedipine, then, appears primarily due to the drug's extracardiac effect of decreasing afterload (302, 306). Although a reflex-mediated increase in resting and exercise heart rate often occurs after nifedipine administration (307), the effect of increased heart rate on myocardial oxygen demand does not appear to be great enough to offset the beneficial decrease in systemic arterial pressure in most treated patients.

A composite analysis of 190 patients treated with nifedipine from eight double-blind placebo-controlled studies indicated that although exertional angina is improved in most patients, anginal symptoms may increase in up to 11% of patients (297-299, 306-310). Whether these increases in symptoms represent fluctuations in the natural history of the disease or are drug induced is uncertain. The reflex increase in myocardial contractility or heart rate, or both, may have been responsible in these patients for the imbalance between oxygen supply and demand. Alternatively, coronary collateral flow may be redistributed in such a way that a coronary steal occurs.

The other Ca^{++} channel blocking agents have also been shown to be efficacious as primary therapy for classic angina. The efficacy of verapamil, in doses up to 120 mg three times a day, as primary therapy has been examined in eight controlled, double-blind clinical trials (226, 228, 311-316). The only study that failed to show a beneficial response was one in which a low dose of verapamil

(80 mg three times a day) was used (313). The other studies demonstrated a significant reduction in the frequency of anginal episodes, nitroglycerin consumption, and improvement in exercise tolerance. The importance of dose for the demonstration of efficacy of verapamil in classic angina was illustrated by the studies of Livesely and colleagues (311) and Sandler and associates (228). High-dose verapamil, 120 mg three times a day, significantly decreased the frequency of angina and prolonged the exercise duration, whereas 40 mg and 80 mg three times a day were no better than placebo.

Perhexiline maleate has also been shown to be beneficial in the treatment of chronic angina pectoris (143). The combined results of seven double-blind investigations that include over 300 patients with classic angina indicate that perhexiline maleate produced a dose-related reduction in the frequency of anginal attacks and in the number of nitroglycerin tablets consumed and an increase in exercise ability (236-239, 317-319). The work done during a stress test increased by 31% from the control test after chronic treatment with perhexiline, 100 mg twice a day (237) and by 77% with 200 mg twice a day (236). In contrast to the findings with nifedipine, perhexiline appeared to exert its antianginal effect by decreasing heart rate at peak exercise while peak arterial pressure during exercise was unchanged (236-239).

Although few controlled, double-blind studies of the use of diltiazem for patients with classic angina have been done, the results generally show less prominent beneficial effects than observed with the other Ca^{++} antagonists. Diltiazem (30 to 60 mg three times a day) improved signs and symptoms of myocardial ischemia in 54% of 59 patients reported in two studies; however, 20% of the patients showed no improvement, and in 26% placebo was more efficacious than diltiazem (320, 321).

Comparison of Calcium Channel Blocking Agents with Other Antianginal Agents: The Ca^{++} channel blockers generally have been found to be as effective as long-acting nitrates and β-adrenergic antagonists in the treatment of classic angina pectoris. Precise comparative efficacy is difficult to assess, however, because the effects of all antianginal agents are dose dependent.

Kaltenbach (322) compared the degree of ST-segment depression that developed during an exercise tolerance test after the administration of a single dose of various antianginal drugs. Nifedipine, 20 mg sublingually, propranolol, 80 mg orally, pindolol, 2.5 mg orally, and nitroglycerin, 0.8 mg sublingually produced approximately the same results; whereas verapamil, 5 mg intravenously, was somewhat less effective and the long-acting nitrates isosorbide dinitrate, 10 mg orally, and pentaerythrityl tetranitrate, 150 mg orally, were much less effective.

Nifedipine appears to be as effective as isosorbide dinitrate for the primary therapy of classic angina (323). Nifedipine, 10 mg three times a day, has been shown to be markedly superior to pentaerythrityl tetranitrate, 30 mg three times a day or 80 mg twice a day (324), or dipyridamole, 75 mg three times a day (309), in decreasing the frequency and severity of anginal attacks, decreasing the need to use nitroglycerin tablets, and in improving performance on an exercise tolerance test.

Propranolol in a dosage of 40 or 80 mg three times a day produces a greater reduction in the frequency of anginal attacks than nifedipine, 10 mg three times a day, whereas propranolol, 20 mg three times a day, is almost equipotent to nifedipine, 10 mg three times a day (323, 325, 326). According to Itoh and associates (327) the reduction in exercise-induced ST segment depression was more pronounced after 10 mg of nifedipine than 20 mg of propranolol. Ekelund (328) found in 26 patients that 10 mg of nifedipine enabled patients to tolerate much greater workloads than 50 mg of metoprolol. The clinical efficacy of nifedipine and beta-blocking agents in classic angina cannot be accurately compared, however, because the complete dose-response curve for each agent has not been ascertained.

Verapamil, 120 mg three times a day, has been shown to be as effective as propranolol, 100 mg three times a day, in decreasing the frequency of angina and nitroglycerin consumption, prolonging the exercise duration, and decreasing the exercise-induced ischemic ST depression (228, 311). In a similar double-blind cross-over study, verapamil, 80 mg three times a day, was shown to be more effective than practolol, 100 mg three times a day (226).

Experience with Combination Regimens: Most of the studies evaluating combined effects of conventional antianginal agents with Ca^{++} channel blockers have been carried out with nifedipine and the β-adrenergic blocking drugs. The combination of 20 mg of nifedipine administered buccally and 20 mg of oral propranolol abolished the increased heart rate usually observed at rest with nifedipine alone (327). With exercise, both heart rate and blood pressure were lower than with either agent alone, and consequently the double product—that is, an index of myocardial oxygen demand—at a given workload was reduced (327). As expected, therefore, a combination of nifedipine, 10 mg three times a day, plus propranolol, 40 mg three times a day, led to a greater decrease in frequency of angina and nitroglycerin tablet consumption than was observed with either agent alone (325). In a similar study design the combination of nifedipine and metoprolol proved to be superior to either drug alone (328). No change in AV conduction was observed in patients on this combination regimen.

Comparisons of combination regimens suggest that propranolol plus nifedipine may be as efficacious as propranolol plus nitrates in the therapy of classic angina. Itoh and colleagues (327) administered propranolol, 20 mg with 10 mg nifedipine or 5 mg isosorbide dinitrate; at rest both combinations caused similar hemodynamic effects. However, during exercise the nifedipine-propranolol regimen caused a greater decrease in heart rate, mean arterial pressure, and double product.

In summary, there is extensive evidence that the Ca^{++} channel blocking agents are effective in the treatment of classic angina pectoris. These agents are comparable to the nitrates and beta blockers as primary therapy, and they appear to be safe and additive when used in combination with the other conventional forms of treatment.

Different pharmacologic approaches of therapy for angina may be more effective than others in a given patient depending on the pathophysiologic mechanism responsible for myocardial ischemia. For example, when fixed obstructive coronary disease is the only mechanism producing ischemia, then propranolol, nitrates, or the Ca^{++} channel blockers, either singly or in combination, may be equally effective. If coronary spasm, however, plays a major role in the genesis of myocardial ischemia the Ca^{++} channel blockers may be more effective than the other forms of treatment because of their relatively greater ability to dilate the coronary arteries.

UNSTABLE ANGINA PECTORIS

Although the role of the Ca^{++} channel blocking agents in unstable angina has not been determined, preliminary evidence suggests they may be useful in that syndrome. Moses and coworkers (329) reported 13 patients with angina and reversible ST-segment changes, most with fixed obstructive coronary disease, who had rest pain refractory to propranolol and long-acting nitrates. The addition of nifedipine (30 to 120 mg daily) abolished rest pain in 85% of the patients. Nifedipine controlled rest pain for a follow-up period up to 6 months; only one patient was refractory to nifedipine and needed coronary bypass surgery. Previtali and associates (330) also reported on 14 patients with fixed obstructive coronary disease with reversible ST-segment deviations and pain. Most of these patients also had a previous history of exertional angina and a positive exercise tolerance test, although seven of the eight patients who underwent ergonovine testing had a positive response. Nifedipine, 60 to 120 mg daily, produced a highly significant reduction in the frequency of spontaneous ischemic episodes. Similar efficacy has been described using verapamil, 480 mg daily, in patients with rest pain and reversible ST-segment changes (331, 332). In some patients with unstable angina and rest pain coronary spasm may clearly play a role in the pathophysiologic mechanism of ischemia and this spasm may be prevented by the Ca^{++} channel blockers. A randomized, prospective, double-blind, multicenter trial of nifedipine as therapy for unstable angina is currently in progress, and its results are awaited with interest.

HYPERTENSION

Because the calcium channel blocking agents are arterial vasodilators, they are potentially valuable in treating systemic arterial hypertension. Alterations of calcium kinetics within vessel walls may also be important in the pathogenesis of arterial hypertension (164, 333, 334). It has been hypothesized, as noted earlier, that increased intracellular $[Na^+]$ may lead to an increase in intracellular $[Ca^{++}]$ and subsequently to a sustained increase of vascular smooth muscle tone (164). In a canine model of renovascular hypertension, nifedipine exerts hemodynamic effects similar to those of hydralazine, that is, it decreases peripheral resistance, lowers systolic and diastolic arterial pressures, increases cardiac output, and elicits a reflex tachycardia and increase in plasma renin activity (335). In contrast to hydralazine, however, nifedipine also reduces coronary vascular resistance, thereby increasing coronary blood flow, and also decreases myocardial oxygen consumption (335). It may prove, therefore, to be particularly suitable for the treatment of hypertension in patients with coronary artery disease.

Clinical studies of the use of the Ca^{++} channel blockers indicate that the degree of blood pressure reduction is directly related to the magnitude of the pretreatment arterial pressure (250, 336) or peripheral vascular resistance (337). For example, in normotensive subjects there may be little or no reduction in blood pressure after a 10-mg oral dose of nifedipine (336) or 5-mg intravenous dose of verapamil (250), whereas in patients with severe hypertension the blood pressure reduction with these doses may be quite marked.

Acute Antihypertensive Therapy: The most obvious value of nifedipine therapy for hypertension has been observed in patients with malignant hypertension complicated by encephalopathy or left ventricular failure (337-341). Guazzi and associates (338) reported experience in three such patients in whom the systemic arterial pressure averaged 307/164 mm Hg and the pulmonary artery pressure, 91/55 mm Hg before treatment. Fifteen minutes after a 10-mg dose of nifedipine was given sublingually the systemic pressure fell to 237/115 mm Hg and the pulmonary artery pressure to 68/35 mm Hg. An additional 10-mg dose of nifedipine produced a continued rapid fall in systemic and pulmonary artery pressures to 176/89 and 47/19 mm Hg, respectively, accompanied by marked symptomatic improvement. The marked antihypertensive effect of nifedipine in hypertensive crises can last for 3 to 4 hours (339, 340).

Chronic Antihypertensive Therapy: The value of the Ca^{++} channel blockers in the therapy of chronic arterial hypertension is not yet clear because of the small number of patients studied thus far (251, 340) or because of the concomitant use of other antihypertensive agents in a noncontrolled fashion (339, 342, 343). Nevertheless, the limited data available suggest that nifedipine is efficacious. A single 10-mg dose of nifedipine or a regimen of 10-mg three times a day or four times a day usually produced a mild to moderate reduction in arterial pressure (337, 340, 342-346). In contrast, a single 30-mg dose of nifedipine decreased the average arterial pressure of 14 chronically hypertensive patients from 177/108 to 123/80 mm Hg (347). As expected, however, heart rate rose from 73 to 85/min in response to the hypotensive effect, and the plasma renin activity doubled. The duration as well as the degree of antihypertensive action of nifedipine is dose related. After a 10-mg dose of nifedipine absorbed buccally the arterial pressure returned towards baseline by 90 minutes; after a 20-mg dose the hypotensive effect was still present at 6 to 8 hours (344). Olivari and associates (345) have shown in 27 untreated patients with essential hypertension that the hypotensive response to a 10-mg oral dose of nifedipine is maximum within less than 1 hour and that the blood pressure approaches the control levels in the subsequent 8 to 12 hours. A dosing regimen of 10 mg every 6 hours provides a consistent reduction in blood pressure (from 198/122 mm Hg con-

trol to 165/97 mm Hg on nifedipine therapy) with only minor hourly fluctuations in blood pressure recorded during a 3-week period (345). There has been no evidence that tolerance develops to the antihypertensive effect of nifedipine.

In contrast to the experience with nifedipine, the hypotensive effect was not sustained in six hypertensive patients during an acute intravenous infusion of verapamil (0.1 mg/kg of body weight followed by 0.0035 mg/kg · min), or in a prolonged trial of 320 to 640 mg daily for 7 weeks (251). Similarly, diltiazem (60 to 90 mg daily) lowered the arterial pressure acutely in patients with hypertension secondary to renal parenchymal or renovascular disease, but after several weeks of chronic therapy the pressure gradually returned to control levels (348).

Combination Therapy: The combination of propranolol or methyldopa with nifedipine produces an additive antihypertensive effect. A single dose of nifedipine, 30 mg sublingually, decreased systolic pressure by 27% and diastolic pressure by 28% (336). Addition of oral propranolol, 0.2 mg/kg of body weight, decreased blood pressure slightly more: Systolic pressure decreased by 32% and diastolic pressure by 30%. In addition, the reflex-mediated increase in heart rate and plasma renin activity observed after nifedipine therapy was abolished by the addition of propranolol. The duration of antihypertensive action of nifedipine (6 to 8 hours) was also prolonged by propranolol (336). Guazzi and colleagues (346) reported on 23 patients with untreated essential hypertension whose arterial blood pressure decreased from 210/126 mm Hg to 170/101 mm Hg while taking 10 mg nifedipine alone every 6 hours for 10 days and to 145/87 mm Hg when methyldopa, 250 mg every 6 hours, was administered concomitantly for an additional 10 days. The antihypertensive efficacy of this drug combination persisted for the 12-month follow-up period.

In summary, the potential role of the Ca^{++} channel blocking agents in the acute and chronic treatment of arterial hypertension clearly requires further investigation. Of the Ca^{++} channel blockers available for clinical use, nifedipine exerts the most potent vasodilatory effect while producing the least adverse electrophysiologic effects. The Ca^{++} channel blocking agents, like the β-adrenergic blockers, may be of particular clinical value in patients with hypertension who also have angina pectoris because of their combined antianginal and antihypertensive effects.

PULMONARY HYPERTENSION

There have been very few studies investigating the use of calcium channel blocking agents in the treatment of pulmonary hypertension. In patients with normal pulmonary artery pressures intravenous verapamil (10 mg bolus or 0.1 mg/kg of body weight bolus followed by 0.005 mg/kg · min infusion) either increased the mean pulmonary artery pressure (205, 208, 349) or caused no change (207, 209, 350). The elevation in mean pulmonary artery pressure from verapamil was considered to be a result of either an increase in pulmonary resistance or a slight reduction in left ventricular function with subsequent increase in left atrial pressure. Landmark and colleagues (351) studied the acute effects of intravenous verapamil (mean dose, 9.6 mg) in 12 adult patients with pulmonary hypertension (mean pulmonary artery pressure, 57 mm Hg) due to primary pulmonary hypertension, congenital heart disease, or pulmonary fibrosis. Verapamil caused a slight, but statistically significant, decrease in mean pulmonary artery pressure and in the work performance of the right ventricle. In some patients, however, verapamil exerted a marked negative inotropic effect with a concomitant increase in the pulmonary arteriolar resistance (351). There were no significant changes in the right atrial pressure, right ventricular end-diastolic pressure, pulmonary arteriolar resistance, cardiac index, or stroke volume.

The calcium channel blocking agents which do not exert as potent a negative inotropic effect as verapamil may be more valuable for the treatment of pulmonary hypertension, but additional studies are needed.

HYPERTROPHIC CARDIOMYOPATHY

In patients with hypertrophic cardiomyopathy the degree of dynamic obstruction to ejection of blood from the left ventricle is directly related to the inotropic state of the myocardium. Beta-adrenergic blockers, which decrease the inotropic state of the myocardium, have been effective as medical treatment for this disorder, but there remain many patients in whom control of symptoms is inadequate. Of the various Ca^{++} channel blockers, verapamil is probably the most suitable for treatment of hypertrophic cardiomyopathy because although it exerts a potent negative inotropic effect, it does not elicit an intense reflex β-adrenergic stimulatory response. Its net inotropic effect, therefore, may be negative if the dose used does not cause significant peripheral arterial vasodilatation.

Kaltenbach and colleagues (352-354) have reported encouraging results with the use of verapamil therapy in hypertrophic cardiomyopathy. Their first study was conducted on 20 patients who had been treated for an average of 20 months with beta blockers. Verapamil, 480 mg orally daily, was then substituted and was administered for an average of 12 months. As compared with the period of treatment with beta blockers, during the period of verapamil therapy there was an impressive improvement in symptoms, a significant reduction in the electrocardiographic signs of left ventricular hypertrophy and a decrease in heart size as ascertained by chest roentgenogram (352). Follow-up catheterization done in 10 patients after treatment with verapamil showed that the outflow tract obstruction had declined in 50% of the patients and that left ventricular mass had decreased in 70% (354). However, left ventricular mass had increased in the other 30% of the patients in spite of verapamil treatment. Rosing and associates (355) also showed in 27 patients with hypertrophic cardiomyopathy that basal and provoked left ventricular outflow gradients diminished in a dose-related manner during an intravenous infusion of verapamil (0.007, 0.014, and 0.021 mg/kg · min). Cardiac output either remained the same or increased slightly in these patients, indicating that the fall

in gradient was due to an actual increase in the effective orifice of the left ventricular outflow tract. No clinically significant increases in mean pulmonary artery wedge or left ventricular end-diastolic pressures were observed during the drug infusions. Hanrath and colleagues (356) suggest that verapamil shortens the abnormally prolonged isovolumic relaxation time observed in hypertrophic cardiomyopathy and may thereby improve left ventricular filling.

Rosing and coworkers (255) directly compared the efficacy of short-term oral administration of verapamil, 80 or 120 mg every 6 hours, and propranolol, 40 or 80 mg every 6 hours, in 19 patients with hypertrophic cardiomyopathy using a prospective, randomized double-blind design. The average exercise capacity on a treadmill increased by 21% to 26% during therapy with either verapamil or propranolol; no difference was noted between the low or high doses of either agent. With time, however, exercise capacity deteriorated in three patients on propranolol therapy but in none of the patients on verapamil therapy. Symptomatically, nine patients considered verapamil the most beneficial agent compared to propranolol and placebo, whereas only three patients considered propranolol to be the most beneficial. Exercise tolerance tests were repeated on eight patients after 3.5 to 6 months of verapamil therapy (120 mg four times a day), and there was an additional 24% improvement in exercise capacity compared to the earlier test after only 4 days of drug therapy. There was a high prevalence of adverse effects in the entire population of 53 patients with hypertrophic cardiomyopathy who were treated with verapamil by these investigators, however. In two patients sinoatrial (SA) or AV node conduction disturbances developed and in two patients, severe myocardial dysfunction developed (255). Although additional studies are needed, verapamil clearly appears promising as an efficacious alternative to propranolol treatment of hypertrophic cardiomyopathy.

PRESERVATION OF MYOCARDIUM

The Ca^{++} channel blocking agents can protect the myocardium from ischemia in a number of ways: By preventing the development of coronary spasm these agents may prevent the occurrence of, or relieve, myocardial ischemia; even in the presence of a fixed coronary occlusion these agents may dilate coronary collateral vessels, thereby enhancing blood flow and oxygen delivery to the ischemic area; through their negative inotropic properties and their ability to reduce afterload, they may decrease oxygen demand, thereby improving the relationship between oxygen supply and demand; and through their ability to block calcium ion flux into cells, the Ca^{++} channel blockers may improve the chances for survival of a cell exposed to a given level of ischemia (55, 357, 358).

The hypothesis that the entry of Ca^{++} into ischemic cells may be harmful is based on the observation that after a period of myocardial ischemia and subsequent reperfusion, excess Ca^{++} accumulates in the cells and localizes as dense bodies within the mitochondria (359). These marked elevations in intracellular [Ca^{++}] are associated with a reduction of high-energy phosphate compounds (ATP, creatine phosphate) which in turn impede intracellular ion transport. The destructive chain of metabolic events provoked by increased intracellular Ca^{++} appears to be partly responsible for the death of cells in the ischemic myocardium (55, 357). Moreover, Henry (358) has shown that there is a direct relation between the quantity of the accumulation of Ca^{++} in the mitochondria and the degree of ventricular stiffness after an ischemic episode. Agents that would inhibit the accumulation of Ca^{++} in ischemic cells might, therefore, help preserve the structure and function of myocardial cells.

There have been numerous studies in experimental animals of the ability of the Ca^{++} channel blocking agent to protect ischemic myocardium during acute myocardial infarction and during cardiopulmonary bypass. Studies are in progress to evaluate the effects in humans.

Effect on Myocardial Infarction: Nifedipine, verapamil, and diltiazem have been shown to alter regional myocardial blood flow after coronary occlusion in the dog and to exert a variable effect on the size and manifestations of myocardial infarction. Nifedipine, for example, has been shown to augment collateral flow into the ischemic myocardium after coronary occlusion and also to decrease infarct size and preserve ventricular function. Dogs receiving nifedipine, 1 mg/kg of body weight daily on a chronic basis, showed increased flow distal to a coronary ligature, particularly in the subepicardium (360). In similar studies administration of nifedipine up to 30 minutes after coronary occlusion increased collateral flow to ischemic areas, decreased infarct size, prevented elevation of left ventricular end-diastolic pressure (361), and improved contraction of the ischemic left ventricular wall (358, 362). Also, nifedipine selectively improved contraction of the ischemic left ventricular myocardium in doses that produced no significant hemodynamic effect (363). In contrast, nitroglycerin and nitroprusside, given in doses adequate to achieve the same degree of afterload reduction, were not associated with similar preservation of left ventricular function (362). Selwyn and colleagues (364) have shown that the ability of nifedipine to limit infarct size is at least in part related to the degree of peripheral vasodilatation produced by the drug. Administration of a low dose (1 μg/kg of body weight) after coronary occlusion improved regional perfusion and produced electrocardiographic and enzyme evidence of decreased infarct size. On the other hand, administration of high doses of nifedipine (13 μg/kg body weight) led to excessive hypotension, reflex tachycardia, and an actual increase in regional ischemia and infarct size.

Verapamil is also effective in increasing coronary blood flow and decreasing infarct size, although its effect on ischemic wall motion is less clear. Studies using verapamil either in low doses (0.005 mg/kg · min infusion) or administered several hours (up to 5) after coronary occlusion demonstrated that although ST-segment elevation was reduced there was no improvement in coronary flow or metabolic indexes of myocardial ischemic (365-368). More recent studies, however, using higher doses of verapamil (0.8 mg/kg body weight) administered immediately before, or within 1 hour of coronary occlusion showed

large (25% to 75%) reductions in the amount of myocardial necrosis (192, 369, 370). The more marked limitation of infarct size, however, required large doses of verapamil (3.5 mg/kg body weight) that depressed myocardial contractility and produced AV block (369). Yet even moderate doses of verapamil (0.8 mg/kg body weight) clearly reduced the amount of myocardial necrosis without an appreciable effect on heart rate, left ventricular end-diastolic pressure, or left ventricular dP/dt.

Although verapamil limits infarct size in experimental animals, its ability to preserve function of ischemic myocardium is less clear than that of nifedipine. In studies on contractility of ischemic myocardium after acute coronary occlusion, verapamil has been shown to preserve postextrasystolic potentiation (371) but did not alter ventricular wall motion in the basal state. In fact, verapamil has been shown to depress selectively the contractility in acutely ischemic myocardium while in the normal myocardium contractility is unaffected (372). Whether this depressed contractility is protective or detrimental is unknown. By decreasing contractility during an acute ischemic event verapamil may limit the myocardial oxygen demands and thereby ultimately preserve myocardial tissue and function.

Diltiazem has also been shown to increase flow to subepicardial ischemic zones after experimental coronary occlusion. Although this augmented flow was associated with a reduction in epicardial ST-segment elevation, no detectable decrease in infarct size has been reported (188). Also, when given to dogs 10 minutes after acute coronary ligation, diltiazem, 0.2 mg/kg of body weight, reduced some of the metabolic consequences of ischemia and preserved contractility in isolated muscle strips (373). Although diltiazem did not protect mitochondrial function in this study (373), Nagao and coworkers (374) have found that a 30-minute pretreatment infusion of diltiazem (20 mg/kg · min) before coronary occlusion resulted in preservation of both mitochondrial respiration and ventricular function during reperfusion.

Effect on the Myocardium After Cardiopulmonary Bypass: The Ca^{++} channel blocking agents may be valuable in protecting the myocardium during the ischemia occurring during open-heart surgery. Using isolated rabbit hearts, Henry and associates (358) found that during an hour of reduced perfusion the ventricle underwent progressive ischemic contracture with the development of increased ventricular pressures. With subsequent high-flow reperfusion, myocardial function remained depressed as evidenced by elevated left ventricular end-diastolic pressure, decreased dP/dt, and decreased systolic pressure. Histologic studies showed a fourfold increase in mitochondrial Ca^{++} at the end of the low-flow period and further marked increase in Ca^{++} accumulation after the high-flow reperfusion period. The addition of nifedipine to the low-flow perfusate prevented ischemic contracture. Also, after the high-flow reperfusion the left ventricular end-diastolic pressure remained low, and there was striking recovery of contractile function. A limited accumulation of Ca^{++} in the mitochondria accompanied this preservation of ventricular function. Using a similar isolated rabbit heart model, Nayler and colleagues (375) found that verapamil (0.5 to 1.0 mg/L) reduced the ultrastructural damage but, unlike nifedipine, failed to prevent ischemic muscle from accumulating Ca^{++}.

Nifedipine also preserves ventricular function in dogs subjected to cardiopulmonary bypass and 1 to 2 hours of total ischemia under either hypothermic or normothermic conditions (358, 361, 376, 377). When nifedipine was given during either the ischemic period or the reperfusion period, stroke-work index and left ventricular dP/dt were significantly improved, and the volume of injured myocardium was only about half that observed in untreated animals. When nifedipine was administered during both the ischemic and reperfusion periods, preservation of myocardial structure and function was even further enhanced (377).

Pretreatment with nifedipine, verapamil, or propranolol (each 2 mg/kg body weight subcutaneously) for 4 or 5 days has been shown to protect myocardial cell function against the deleterious effects of global ischemia and reperfusion (378). These three agents were equally effective in reducing mitochondrial and tissue Ca^{++} accumulation, preserving mitochondrial respiration, and preserving myocardial function.

Potassium is frequently used in cardioplegic solutions to preserve myocardial function during cardiopulmonary bypass and total myocardial ischemia. It has been proposed that K^+ serves as a physiologic Ca^{++} channel blocker that can protect the heart against the deleterious effects of an overload of Ca^{++}. Magee and colleagues (379) compared a solution of KCl (37 meq/L) and two concentrations of nifedipine (10 and 100 μg/dL) as cardioplegic solutions during hypothermic ischemic arrest. Although the low dose of nifedipine was not protective, the high dose was as effective as K^+ in protecting the functional capacity of the left ventricle.

Summary

Calcium ion fluxes play a major role in several fundamental physiologic processes of the myocardial cell. The slow inward current of the cardiac action potential is carried principally by Ca^{++} ions and links surface excitation to muscular contraction. The magnitude of the slow inward current can be augmented by catecholamines and diminished by metabolic inhibitors and Ca^{++} channel blocking agents. The investigational drugs nifedipine, verapamil, diltiazem, and perhexiline are potent agents capable of blocking Ca^{++} influx into the cell and are greatly expanding the cardiovascular therapeutic armamentarium. The exact site and mechanism of action of these drugs remain unclear and may vary among the different compounds. Verapamil has proved useful in treating various supraventricular rhythm disturbances including re-entrant paroxysmal supraventricular tachycardia, atrial fibrillation, and on occasion atrial flutter. It should be administered cautiously to patients with abnormal function of the SA or AV nodes because it may suppress impulse initiation and conduction.

The Ca^{++} channel blocking agents are potent dilators

of coronary and peripheral arteries, and in isolated tissue preparations they exert potent negative inotropic, chronotropic, and dromotropic effects. In intact animals the peripheral arterial vasodilatation induces reflex-mediated adrenergic activity that opposes the direct negative inotropic, chronotropic, dromotropic, and hypotensive effects. The net hemodynamic and electrophysiologic effect of these agents, therefore, results from a complex interplay of both direct and reflex phenomena. Nifedipine is the most potent arterial vasodilator and is consequently associated with the most intense reflex adrenergic activity. The net effect of nifedipine, therefore, is that of relatively pure vasodilatation with little electrophysiologic or inotropic effect. On the other hand, doses of verapamil and diltiazem that produce the same degree of vasodilatation as nifedipine produce greater negative dromotropic effects, and the reflex-induced β-adrenergic activity may not completely offset these direct electrophysiologic effects.

Nifedipine, diltiazem, and verapamil have been effectively used to prevent coronary spasm in Prinzmetal's variant angina. The clinical efficacy of the Ca^{++} channel blocking agents in classic angina is related to their ability to decrease afterload, myocardial contractility, and heart rate and to increase coronary blood flow. Nifedipine can be used safely in combination with β-adrenergic blocking agents. The negative inotropic effects of verapamil are valuable in improving the symptoms and hemodynamic disturbance of hypertrophic cardiomyopathy. The Ca^{++} channel blockers may also be used in treating arterial hypertension, unstable angina pectoris, acute myocardial infarction, and cardiopulmonary bypass, but their exact role in therapy of these conditions needs to be elucidated.

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NIFEDIPINE THERAPY FOR CORONARY-ARTERY SPASM

Experience in 127 Patients

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Abstract We report clinical experience with the coronary vasodilator nifedipine in 127 patients with symptoms of myocardial ischemia associated with electrocardiographic or angiographic evidence, or both, of coronary-artery spasm. In the majority of patients conventional antianginal therapy including nitrates and beta-adrenergic blockers failed, and in one third of the patients at least one episode of ventricular tachycardia developed during an attack of angina. Nifedipine (40 to 160 mg every 24 hours) significantly reduced the mean weekly rate of anginal attacks from 16 to two (P<0.001). Similar marked reductions in the nitroglycerin requirement were noted. In 63 per cent of the patients complete control of anginal attacks was achieved, and in 87 per cent the frequency of angina was reduced by at least 50 per cent. Nifedipine was generally well tolerated, with only 5 per cent of the patients requiring termination of the drug because of intolerable side effects. This experience with nifedipine suggests that it is a highly effective drug for the treatment of coronary-artery spasm and variant angina. (N Engl J Med. 1980; 302:1269-73.)

INTEREST in coronary-artery spasm has recently been heightened by evidence suggesting that spasm has a fundamental role in some forms of ischemic heart disease and by the availability of potent coronary spasmolytic agents.[1-17] The dihydropyridine derivative nifedipine belongs to the class of coronary vasodilators that appear to exert their effect by inhibiting the slow calcium current responsible for the contraction of vascular smooth muscle.[18] Initial reports of its effectiveness in limited groups of patients with documented coronary spasm have been quite encouraging.[19-24] Since 1974, nifedipine has been available in the United States for use on an investigational basis. We report here the results of the experience with nifedipine in 127 patients with coronary spasm treated with this agent.

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These results were presented in part at the 52d Scientific Session of the American Heart Association, Anaheim, Calif., November 12-15, 1979.

METHODS

All 127 patients in the study had severe recurrent attacks of angina at rest. In addition, all patients met one or both of the following criteria considered indicative of coronary-artery spasm[7,14,15,25,26]: one or more episodes of severe angina at rest associated with reversible ST-segment elevation in at least two leads of the electrocardiogram (other than aVR), and spontaneous or ergonovine-induced coronary-artery spasm observed during coronary angiography in association with either typical ischemic chest pain or ST-segment shifts on the electrocardiogram. In accordance with the criteria of Chahine et al.,[7]

> Coronary artery spasm was considered to be present only when the evidence was unequivocal and satisfied two of the following three criteria: 1) appearance of transient narrowing in a coronary segment that initially or subsequently appeared to be angiographically normal; 2) occurrence of transient total obstruction in a normal coronary segment or at the site of partial narrowing due to an atheromatous lesion; 3) prompt response of the narrowing or obstruction to sublingual administration of nitroglycerin or its spontaneous relief, documented upon subsequent injections of the same coronary artery.

These 127 patients (60 men and 67 women) were treated between 1974 and 1979 and were the subjects of the observations on which this study is based. The mean age was 52 years and ranged from 30 to 84 years. Seventy-five per cent of the patients were less than 59 years of age. Sixty-eight patients (54 per cent of 127) had both angina at rest with reversible ST-segment elevation and spasm at angiography. Thirty-seven patients (29 per cent) were included in the study on the basis of angina at rest associated with reversible ST-segment elevation. In 22 patients (17 per cent) coronary-artery spasm was noted at angiography in association with angina, but ST-segment elevation was not detected in the lead being monitored.

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Of these 22 patients, five had coronary arterial obstructions of at least 50 per cent of the lumen of one or more major coronary arteries.

Before initiation of nifedipine therapy, 20 patients had sustained a myocardial infarction and eight had undergone coronary revascularization. Arrhythmias had been recorded during one or more attacks of coronary spasm in 74 patients (58 per cent). Ventricular tachycardia had occurred in 43 patients (34 per cent), and ventricular fibrillation in 17 (13 per cent). Of the 127 patients, 121 (95 per cent) underwent coronary angiography before nifedipine was started. Fifty-two (43 per cent) of the 121 patients were considered to have at least a 50 per cent fixed luminal narrowing in one or more of the major coronary arteries. Twenty-four patients (20 per cent of 121) had obstruction of less than 50 per cent of the lumen; forty-five (37 per cent) had what appeared to be angiographically normal coronary arteries.

The medical therapy received by the patients before initiation of nifedipine is summarized in Table 1. All patients underwent a course of conventional antianginal therapy with the agents and dose ranges shown in Table 1. The 127 patients in this study were considered to be candidates for treatment with nifedipine when conventional therapy was found to be ineffective, only partly effective, or not well tolerated.

Nifedipine was supplied to the patients in the form of 10-mg light-protected capsules to be taken orally (provided by the Pfizer Pharmaceutical Corp., New York, New York). In all cases written informed consent was obtained with forms that had been approved by institutional review committees.

We evaluated the response to nifedipine by comparing the number of anginal attacks per week at various periods before and during therapy. In addition, the mean weekly attack rate for a two-month period before initiation of nifedipine was compared with the mean weekly attack rate during the entire period of observation of each patient during nifedipine therapy. In a manner similar to that employed to analyze the number of attacks, the number of sublingual nitroglycerin tablets required was analyzed as another index of therapeutic effect.

Data were analyzed on an ITEL AS/7031 computer system with the SAS statistical package. Statistical methods consisted of standard two-tailed t-tests for unpaired and paired data, Wilcoxon rank-sum tests for unpaired data, and signed-rank-sum tests for paired data.

Results

Daily doses of nifedipine ranged from 40 to 160 mg and averaged 64 mg. The mean duration of nifedipine treatment was nine months (S.E.M. = 0.8 months), the median six months, and the range three days to 45 months. One hundred sixteen (91 per cent) of the 127 patients were followed for more than two months.

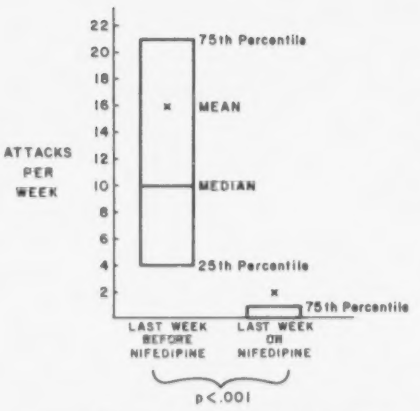

Figure 1. Response to Nifedipine in 127 Patients.
The mean number of anginal attacks per week dropped significantly after nifedipine. x denotes the mean value.

The number of anginal attacks at various periods before and during therapy are shown in Figures 1 through 3. The number of attacks fell strikingly from a mean of 16 in the week before initiation of nifedipine to a mean of two in the last week of observation during nifedipine therapy (Fig. 1). Since the data do not follow a Gaussian distribution, the 25th and 75th percentiles as well as the median are displayed rather than the standard deviation or standard error of the mean. The decrease in frequency of anginal attacks with nifedipine was statistically significant ($P<0.001$) according to the signed-rank-sum test for paired data.

The number of sublingual nitroglycerin tablets used fell from a mean of 22 in the week before initiation of nifedipine to a mean of two during the last week of observation during nifedipine treatment. Comparisons were also made between the mean weekly usage of nitroglycerin for a two-month period before nifedipine was begun and the entire period of

Table 1. Medical Therapy before Initiation of Nifedipine.*

Drug	No. of Patients Receiving Drug †	Dosage per 24 Hours	Drug Partly Effective	Drug Ineffective	Increased Frequency of Anginal Attacks with Drug
			number of patients		
Propranolol	84 (66)	40–480 mg	16	58	8
Isosorbide dinitrate	96 (76)	20–480 mg	46	43	2
Nitroglycerin paste	89 (70)	1–24 in (2.5–60 cm)	39	42	1
Phenoxybenzamine	17 (13)	20–160 mg	3	12	2
Phentolamine	4 (3)	50–100 mg	1	3	—
Perhexilene	1 (1)	200–500 mg	1	—	—
Verapamil	3 (2)	240–560 mg	1	1	—

*Since the dose of the above medications varied with time in individual patients, the values shown represent the range of doses employed.
†Numbers in parentheses represent percentages of the entire series of 127 patients.

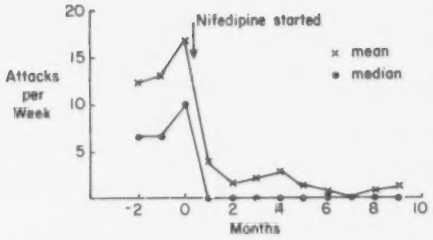

Figure 2. Mean and Median Weekly Attack Rates at Various Times before and during Nifedipine Therapy.
A prompt, dramatic, and sustained decrease in attack frequency occurred during nifedipine treatment.

observation during nifedipine treatment. All analyses showed marked changes after initiation of nifedipine, similar to that shown in Figure 1 ($P<0.001$ for all individual comparisons considered independentiy).

Figure 2 illustrates the mean and median weekly attack rates at various times before and during long-term therapy with nifedipine. Both curves show a marked, sustained decrease in attack frequency.

The distribution of responses to nifedipine is shown in Figure 3. Sixty-three per cent of the patients had a 100 per cent decrease in the frequency of attacks, and 110 patients (87 per cent) had at least a 50 per cent reduction in the frequency of attacks. Only 4 per cent of the patients had less than a 10 per cent decrease in attack frequency. Two patients had a 50 per cent or greater increase in attack frequency while taking nifedipine.

Analyses were performed to determine whether the response to nifedipine varied in particular subsets of patients. The presence or absence of high-grade fixed lesions or concurrent therapy with isosorbide dinitrate or propranolol did not alter the response to nifedipine. In the subgroup of patients with coronary-artery obstructions of less than 50 per cent of the lumen and both angiographic evidence of coronary-artery spasm and ST-segment elevation on the electrocardiogram, 60 per cent had a 100 per cent decrease in the frequency of attacks, and 89 per cent had at least a 50 per cent reduction in the frequency of attacks.

The findings in the 17 patients who did not have at least a 50 per cent decrease in attack frequency were analyzed. Seven of these patients received what may be considered adequate nifedipine therapy (i.e., at least 80 mg per day) at appropriate intervals (no more than six hours between doses) and represent true failure of nifedipine therapy. The remaining 10 patients did not receive an adequate course of nifedipine, and their lack of response was considered a possible failure of nifedipine therapy; in six of these patients an adequate dose could not be administered because of intolerable side effects. It was of note that in the 72 of 127 patients who were treated with less than 80 mg of nifedipine per day, 68 per cent had a 100 per cent decrease in the frequency of attacks, and 96 per cent had at least a 50 per cent decrease in the frequency of attacks.

Nifedipine was terminated in 20 patients (16 per cent of 127) for a variety of reasons. In three patients therapy was terminated after the development of a myocardial infarction, and in five patients after coronary-artery-bypass grafting. In nine cases (7 per cent) nifedipine was terminated because the investigator considered it ineffective in controlling the patient's anginal attacks. One patient was lost to follow-up, and one died during nifedipine therapy. Side effects were noted in 50 patients (39 per cent) but were severe enough to require discontinuation of nifedipine in only six (5 per cent of 127) (Table 2). The most common side effect was dizziness, which occurred in 13 per cent of patients. Flushing, pedal edema, and postural hypotension were next most common in frequency. Dizziness, flushing, and headache were the side effects that most frequently led to termination of therapy and resulted in an inadequate trial of nifedipine. In one patient a generalized rash also developed, and in two others muscle cramps occurred. In all

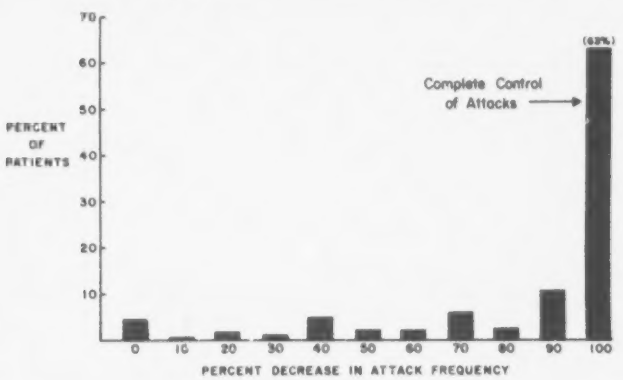

Figure 3. Distribution of the Decrease in Attack Frequency from Pretreatment Levels to the Last Week of Observation during Nifedipine Treatment in 127 Patients.

Table 2. Side Effects of Nifedipine in 50 Patients (39 per Cent of Study Population).

Side Effect	Frequency of Occurrence *
Dizziness	13 †
Flushing	11 †
Pedal edema	9
Hypotension	6
Paresthesias	4
Weakness	4
Headache	3 †
Muscle cramps	2
Nausea	2
Palpitations	2
Rash	1
Other	9

*All values represent percentages of the entire population of 127 patients.

†Side effects that most frequently led to termination of therapy and resulted in an inadequate trial of nifedipine.

patients side effects resolved with the discontinuation of nifedipine.

Discussion

In the 127 patients who form the basis of this report, spasm of a major coronary artery was diagnosed on the basis of characteristic angiographic or electrocardiographic changes, or both, in association with chest pain typical of ischemia. The group is similar to that described by Prinzmetal et al. in 1959 as having a "variant" of classic angina.[27] Since that original description it has been found that variant angina can occur in patients with fixed coronary stenoses and in patients with angiographically normal coronary arteries.[2-8] Arteriography performed during an attack of chest pain has proved that the syndrome is caused by coronary vasospasm, as originally proposed by Prinzmetal.[6,27]

Attacks of variant angina are often associated with potentially life-threatening arrhythmias and may be fatal.[17] Indeed, the occurrence of ventricular tachycardia and ventricular fibrillation had been documented in 34 per cent and 13 per cent, respectively, of the patients in this study.

In the past, long-acting and short-acting nitrate preparations have been the mainstay of therapy for coronary spasm.[17] Neither propranolol nor coronary-bypass surgery has been as useful for variant angina as for classic angina.[17,28] A number of other agents with a multiplicity of pharmacologic actions have been used, but there remain patients, such as the majority in the present study, whose attacks cannot be controlled with conventional therapy.

Calcium-channel blocking agents, a new group of powerful coronary vasodilators, offer a promising new approach to the therapy of coronary spasm. The agents with which the most clinical experience is available are nifedipine,[19-24] verapamil,[29,30] perhexilene,[31-33] and diltiazem.[34] A report by Endo et al. from Japan suggested that nifedipine was extremely effective in controlling coronary spasm.[35] Findings in a limited number of patients in the United States supported these observations.[22-24]

In this report we have summarized the results obtained in 127 patients with coronary spasm who had a high weekly rate of anginal attacks, high nitroglycerin requirements, and a relatively high incidence of ventricular tachyarrhythmias. In these patients the attacks could not be prevented by conventional antianginal therapy that included long-acting nitrates or beta-adrenergic blocking agents, or both (Table 1).

Nifedipine produced a prompt, sustained, dramatic decline in the frequency of anginal attacks and the requirements for nitroglycerin. Nearly two thirds of the patients gained complete control of their anginal attacks (Fig. 3). Only 13 per cent of the patients did not have at least a 50 per cent reduction in the frequency of anginal attacks. In only 7 per cent of patients was the drug considered ineffective and discontinued.

In summary, this experience with nifedipine reveals an impressive reduction in the frequency of anginal attacks and the nitroglycerin requirement in a large group of patients with coronary spasm. However, there are certain theoretical limitations to this study: it was not a randomized or blinded trial, and the natural history of coronary spasm among patients is highly variable. However, several important positive features of this study do indicate that the observed improvement is due to nifedipine therapy: first of all, the attacks of myocardial ischemia were documented objectively by means of angiogram or electrocardiogram, or both; secondly, these patients did not respond to conventional therapy, including long-acting nitrate preparations; thirdly, the period in which there was no response to conventional therapy provided for each patient a control level of attack frequency that was then compared with the attack frequency observed during nifedipine therapy; and finally, the reductions in attack rate and nitroglycerin requirement were extremely marked and sustained. These features suggest strongly that nifedipine provided chronic suppression of coronary spasm not attainable with conventional therapy.

The success achieved with nifedipine in these patients with coronary spasm has implications beyond the treatment of variant angina, a relatively rare disease. It is now recognized that coronary spasm may have a role in other, more common forms of ischemic heart disease. The potent, long-acting spasmolytic action of nifedipine demonstrated in this study could well be of benefit in the treatment or prevention of chronic stable angina, unstable angina, and acute myocardial infarction.[1,11,12,36,37] These questions may be answered by the numerous studies of nifedipine that are now in progress.

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Mr. SCHEUER. Thank you very much, Dr. Antman.

You mentioned the calcium-blocking drugs. Why are the calcium blocking drugs being brought into the U.S. market so long after their free availability in European countries?

Dr. ANTMAN. Well, I think it relates to the amount of data which are required by the FDA before the drug can be brought forth onto the market here. Let me give you an example about verapamil versus nifidepine.

They are both calcium blockers, and it is conceivable they both could be effective against abnormal heart rhythms. It turns out that verapamil is the only one which is really effective against abnormal heart rhythms in the clinically relevant doses that we would be talking about——

Mr. SCHEUER. Where was that developed?

Dr. ANTMAN. Verapamil, I believe, was developed in Germany as well.

Mr. SCHEUER. As well as what?

Dr. ANTMAN. As nifidepine, which was also developed in Germany.

For example, there were a number of studies in England which tested nifedipine versus verapamil for their ability to control abnormal heart rhythms, and it turned out that verapamil was the effective one. Yet the same studies are likely to have to be repeated in the United States when they were already performed in a reputable laboratory overseas with data which could be used to make that judgment.

Mr. SCHEUER. Are those two drugs freely available here in this country?

Dr. ANTMAN. No. Both nifedipine and verapamil are still investigational in this country. I believe both of them have been recommended for approval by the advisory boards on the cardiorenal sections of the FDA, but as yet they have not been formally approved.

Now, it is also my understanding that verapamil will be approved as an intravenous preparation for treatment of abnormal heart rhythms. There is an oral preparation which is effective for angina and for abnormal heart rhythms but that's a long way off from approval.

Nifedipine will be approved, I believe, for angina pectoris, both chronic stable angina and angina which is believed to be related to spasm of coronary arteries.

Mr. SCHEUER. How long have these two drugs been used abroad in Europe?

Dr. ANTMAN. Well, they were brought out for clinical investigation in Germany in 1970, so we have a decade of data beginning in Germany, and then a number of other countries. For example, in 1976 it was available in Mexico and Japan, and a number of patients travel outside the United States, for example to Mexico, where they receive a prescription for nifedipine and obtain the drug there. Then they come back to this country and take the pills here under the care of a physician essentially outside of our country.

Mr. SCHEUER. That's the oft-repeated tale.

Would you like to comment generally, just sort of taking off from that as a point of departure, on the drug-approval process in the

United States, its strengths and its weaknesses. Particularly, you might compare it to the advanced developed countries in Europe and Asia.

Dr. ANTMAN. Well, I think its strength is that it's cautious, and it is unlikely that with a cautious approval system we would run into a problem with a drug that had a number of serious side effects that were unknown or unsuspected.

The disadvantage is the cumbersome nature of the regulatory process. Essentially the length of time that it takes to go from the synthesis of a drug to the final marketing of that drug I think is a very cumbersome process for the manufacturer, for the physican, and essentially the patient suffers because earlier availability of the drug would alleviate suffering from a number of conditions

Mr. SCHEUER. Congressman Gore.

Mr. GORE. Thank you very much, Mr. Chairman.

Doctor, you went through the history of nifedipine. The other countries that have recently approved nifedipine, Sweden for example, do these other countries normally allow the use of data from validated foreign studies in their approval processes.

Dr. ANTMAN. I have given you a long list of countries there, and I'm not sure which ones would answer that in the affirmative. My suspicions are that, amongst that list there will be certain countries that utilize the data already available from other countries.

Mr. GORE. Do you think we should do that?

Dr. ANTMAN. Absolutely. As long as we understood that it was a reputable laboratory and we could establish a task force of scientists or professionals who could monitor the laboratories that we were willing to take data from——

Mr. GORE. Yeah; well, that's my feeling, also. I think that our research dollars and our laboratory facilities are far too limited to ignore work that is already done in qualified clinical labs elsewhere in the world, if we can assure American citizens that we are accepting data only from reputable laboratories and that we are verifying the work or the reputation and capabilities of those facilities.

Dr. ANTMAN. I would agree with that.

Mr. GORE. Now, you mentioned the availability of information about breakthrough drugs like calcium blockers to practitioners across the country. Should we have a central repository of some kind——

Dr. ANTMAN. Absolutely.

Mr. GORE [continuing]. That doctors could access?

Dr. ANTMAN. Absolutely. I think that would be a very helpful idea. The only sources a physician in practice now has to obtain information about a new drug include the literature, other physicians, and national meetings where these drugs are discussed. If there was a source that a practicing physician could tap, I think it would be very helpful. I think a computer link might be a way to get at that.

Mr. GORE. Doctors are burdened like all other professionals with an enormous surplus of information in today's modern society, and it is unreasonable to suppose that doctors can keep up with all of this information on a general basis and have it in the back of their

minds when a particular patient with a particular need comes in and presents himself or herself for treatment.

If we can come up with an information system that will allow physicians in this country to access available data about a particular problem when it occurs, and include in that repository information on breakthrough drugs like the ones that are under discussion here, then we will help the physician, we'll help the patient, and we'll help the drug companies as well, because the market for these new products will be larger, quicker. We won't have to wait. So I would hope that by working together our two subcommittees can come up with a recommendation in that area.

Now, when a cardiac drug has been approved for one clinical indication, would you agree that it is unnecessary to redo all of the testing when it is proposed for use for another indication?

Dr. ANTMAN. I think you would have to analyze that individually for various classes of drugs, but in general that is probably correct.

Mr. GORE. Safety testing.

Dr. ANTMAN. Safety and efficacy. An example of that would be the beta adrenergic blocking drugs. There are three which are approved in the United States. They are propanalol, metoprolol, and nadalol, three beta blockers which have differences in chemical structure and in dosing requirements. Propanalol has been around the longest, and is approved for angina, hypertension, arrhythmias, prophylaxis against migraine headaches, against a condition known as pheochromocytoma in which there are intermittent bursts of catecholamines discharged into the blood, and finally, hypertrophic cardiomyopathy. And yet metaprolol and nadolol are only approved for hypertension. Nadolol is also approved for angina.

It is conceivable that these other drugs would also be effective for these other conditions. I think the information is probably available. But if we require that each drug, each new drug in a general class, goes through the same efficacy testing as the index drug did for that class, I think we are going to delay approval of these new drugs for multiple indications.

Mr. GORE. Now, you have commented on the use of validated data from reputable foreign facilities. In addition to that recommendation, which I agree with, are there any other problems that particularly adhere to cardiac drugs and the new breakthrough of cardiac drugs that you would like to see dealt with?

Dr. ANTMAN. I think the cooperative nature is something I would like to emphasize again, because if each institution that has the drugs available for clinical investigation studies, let's say, 20 or 30 patients, there is a limited amount of information that one can gain and a limited statistical statement that one can make. But if you pool the data from a number of institutions, then you have a much more powerful statement that you can make.

It is important for all drugs, and especially for cardiovascular drugs, where potential adverse effects and drug interactions are important to know about.

Mr. GORE. Thank you very much.

Thank you, Mr. Chairman.

Mr. SCHEUER. Just following up on your recommendation for pooling the data, do you think there should be some kind of central computerized bank into which all of these disparate small groups

of researchers that you mentioned before would plug in their information and then it would be subject to retrieval?

Dr. ANTMAN. Yes; I think we are underutilizing the technology which is potentially available to us. If we have enough technology to make a pinpoint landing of a space shuttle, I think we have enough technology to provide access to drug information, drug interactions, which would be a very helpful thing for the practicing physician.

Mr. SCHEUER. Thank you.

Congressman Carney.

Mr. CARNEY. Doctor, this has been such a great hearing, I am really caught up in this whole thing.

I do have a question, though. My colleague, Mr. Gore, asked about using a drug that has been approved for one clinical indication. Is there much going on in the practice of medicine where it is commonly felt that this drug has a good effect on another clinical application but hasn't been approved and perhaps they'll treat the patient with that drug, saying they're treating him for the first indication?

Dr. ANTMAN. That probably occurs.

Mr. CARNEY. Does that help—I mean, it probably helps the patient, but does that help the prospect of having that drug approved for the second clinical application?

Dr. ANTMAN. No, not the way the process exists at the present, because one has to document the effectiveness for that second indication. If you're technically giving it for the first indication, which is already an approved indication, then you haven't formally documented the efficacy for the second indication. It is only until efficacy is documented for the other indications that they will officially be approved.

Mr. CARNEY. Perhaps this is not a good line of questioning to ask, but do you think—once again we use that hypothetical situation where they are giving it for one indication in reality and in the back of the physician's mind he is trying to help another indication—is there much clinical evidence that could be gained by him just following through and saying, "Hey, by the way, it has a side effect and we seem to be——

Dr. ANTMAN. Sure, absolutely. I think you gain information anyplace you can.

Mr. CARNEY. In other words, that's what you're forced to do in the practice of medicine today because of the backlog or because of the intricacies of having a medication approved for a second utilization; is that correct?

Dr. ANTMAN. I think that's right.

Mr. CARNEY. Would you quickly give me a definition of a beta blocker?

Dr. ANTMAN. OK. There are a number of receptors throughout the body which have been classified into alpha and beta receptors. Essentially, the beta receptors are two types—one is involved in stimulating the heart rate and the force of heart contraction, that's beta 1; and beta 2 receptors are involved in dilating blood vessels and dilating the bronchial airways and regulating blood sugar levels.

When a drug is available which blocks a beta receptor, we call it a beta adrenergic blocking drug, and it will counteract the effect of stimulation of that receptor.

An example of——

Mr. CARNEY. That would be a beta 2 drug dealing with the dilation of—

Dr. ANTMAN. Yes; let me give you an example of a naturally occurring compound which might be—made by the body naturally, and might stimulate a beta 1 receptor for increased force of cardiac contraction, adrenalin, for example. If we had a blocker for that receptor, a beta 1 blocker, it would block the effect of adrenalin on the heart muscle. So we have a beta stimulant and a beta blocker. The beta stimulant is made endogenously by the body. When that system goes out of control, we give a drug which is a beta blocker, which inhibits the excess effect of the body's natural system.

Mr. CARNEY. OK. That would be beta 1, then, right?

Dr. ANTMAN. Beta 1 controls the force of heart contraction, and beta 2 controls blood vessel tone.

Mr. CARNEY. You would be blocking a natural body function to dilate the blood vessel, is that correct?

Dr. ANTMAN. Depending upon which kind of drug you gave—if you gave a drug which was specific for one of the beta blockers, you would have an effect relative to that beta receptor only. For example, metaprolol is a cardio-specific beta blocker and will block beta 1 receptors more than beta 2 receptors, and therefore can be safely given to a patient who has asthma.

Mr. CARNEY. I have another question. In your outline you mention that you can use antiarrhythmic agents to prevent sudden cardiac deaths; is that correct?

Dr. ANTMAN. That's right.

Mr. CARNEY. Are you talking about applying that agent after someone has initially had some sort of heart malfunction and is in a clinical situation?

Dr. ANTMAN. There are 400,000 to 500,000 people a year who have an episode of sudden cardiac death, and that is due to a fatal cardiac arrhythmia. Now, when they are resuscitated, they are then evaluated, and if that fatal cardiac arrhythmia occurred not in the setting of a heart attack, or myocardial infarction, there's about a 30-percent chance that within the next 12 months a repeat fatal arrhythmia will occur. This is a population of patients who are high risk, therefore, for these attacks of sudden cardiac death.

The antiarrhythmic agents which are available, both the standard ones which are currently available and the investigational ones, are particularly potent in preventing this. But one cannot at this point predict which agent the patient will do best with. Therefore, you have to test a series of agents. Once you start getting into the investigational agents, one gets into the bulk of forms that have to be filled out and it is extremely cumbersome to treat a patient long term with this large series of forms that have to be kept up to date on every routine visit.

Mr. CARNEY. Would the medication have an effect on someone who died from sudden cardiac death caused by a myocardial infarction?

Dr. ANTMAN. Yes.

Mr. CARNEY. Not just by arrhythmia?

Dr. ANTMAN. Oh, I see. Well, no, the antiarrhythmic agent would be effective against abnormal heart rhythms, be they occurring not in the setting of a heart attack or in the setting of a heart attack. People can die in the setting of a heart attack from something other than an abnormal heart rhythm—shock, essentially, and poor heart contraction.

Mr. CARNEY. What I was thinking of—and I was just trying to stretch this out, maybe down the road 20 years from now—was using that in a certain segment of the population before they had that problem. Is that possible, before you——

Dr. ANTMAN. It's theoretically possible, but——

Mr. CARNEY. But that's not what you're looking at now?

Dr. ANTMAN. No; we are now tailoring the drugs to the individual patient.

Mr. CARNEY. The problem that you're having is the enormous amount of paperwork required to use that type of application——

Dr. ANTMAN. That's right.

Mr. CARNEY [continuing]. Clinically now because of FDA parameters that are set?

Dr. ANTMAN. That's right. I have talked to you about the half-a-million people a year who have sudden cardiac death, and we haven't even begun to touch the large population of patients who have symptoms due to abnormal heart rhythms but haven't had an episode of sudden cardiac death. They, too, could benefit.

Mr. CARNEY. That's right. You're talking about millions of people who could have some sort of benefit.

Dr. ANTMAN. That's correct.

Mr. CARNEY. With time being the way it is, I will yield back my time to the Chair.

Mr. SCHEUER. Mrs. Schneider.

Mrs. SCHNEIDER. I am sure you gentlemen have asked all my questions already, so I would be happy to move on.

Mr. SCHEUER. OK. I'm going to ask one more question. Would it be your view that the investigational and compassionate use of the new cardiovascular drugs imposes a real burden on physicians?

Dr. ANTMAN. Could you amplify that?

Mr. SCHEUER. All right. Do you believe that the compassionate use of the new cardiovascular drugs—let's say a drug that's available abroad, for a variety of reasons is the best drug for a particular patient and it hasn't been approved in this country, so you make a compassionate application to use that drug—has that been a successful process in your view?

Dr. ANTMAN. Well, not really. Dr. McMahon explained to you the reason why. He was essentially getting a compassionate IND there for a specific patient, which happened to be himself, for a specific indication. He told you about his position on that.

Mr. SCHEUER. Would that be typical of your experience?

Dr. ANTMAN. That would be typical when you deal with specific patients or a limited number of patients. If you want to do this on a large scale, it requires tremendous staffing. Now, it's possible to do it, but it's a very time-consuming task.

Mr. SCHEUER. I just put in a piece of legislation today, cosponsored by Congressman Carney of New York, that we both hope will correct that situation.

Dr. ANTMAN. I hope so.

Mr. SCHEUER. The hour is late and we went far beyond what we had thought we had alloted to you, Dr. Antman. It is evidence of how stimulating we found your testimony. You have really testified like an old pro at congressional hearings, but I am informed by my staff that this is your first appearance.

Dr. ANTMAN. Yes, sir, it is.

Mr. SCHEUER. You were really quite good and very impressive to all of us. Thank you very, very much.

We will now have our last panel of the evening, and we will go over 15 minutes so that we'll have a good 30 minutes with this panel.

This is a panel on prostaglandins. We will hear from Dr. Andre Robert of the Upjohn Co., and Richard E. Faust of Hoffmann-LaRoche.

STATEMENTS OF DR. ANDRE ROBERT, M.D., SENIOR SCIENTIST, THE UPJOHN CO.; AND RICHARD E. FAUST, DIRECTOR OF RESEARCH PLANNING AND DEVELOPMENT, HOFFMANN-LA ROCHE, INC.

Dr. ROBERT. Well, I would like to tell you where we stand in the area of prostaglandins as they relate to the functioning and the diseases of the digestive system.

To begin with, I will briefly summarize how we came about to have prostaglandins. They are natural substances. They were discovered more than 40 years ago, first in seminal fluid, in Sweden. Then the studies became dormant and for a few years not much more was done with the prostaglandins because these were the war years.

Soon after the war, again in Sweden, studies were resumed and scientists there began to look again at the prostaglandins. Up to that time there were only extracts. No one knew exactly their chemical structure. But in the midfifties, when work was continued in Sweden, their chemical composition was uncovered. Not only were they identified as chemical entities, but they were also synthesized, in very small amounts in those days.

This was enough, however, to discover some of their properties. It was found that they have a wide range of biological activities. They affect almost every system in the body.

This is not surprising, because we found later on that we can extract prostaglandins from practically every tissue. It seems that every cell contains prostaglandins. It is not surprising, in retrospect, that when they are administered to animals and to humans, that we find a variety of activities.

After their chemical structure was discovered in the midfifties, several scientists, chemists mostly, began to synthesize them in greater quantities and also to modify the original molecule, to make new prostaglandins that would be more potent longer acting than the natural prostaglandins, and that they might act orderly.

We didn't know then if this would be the case, but there was the hope.

In the midsixties, many of these scientists happened to be at Upjohn where they devoted a large amount of effort in the synthesis of these prostaglandins, both the natural and the what we call the analogs, which are derivatives of the natural prostaglandins.

Then with the increased supplies of prostaglandins due to new chemistry, we began to study more closely their biological properties.

What I would like to tell you about is only what I have worked on myself; their effect on the digestive system, which are quite remarkable.

In the first place, some of the natural prostaglandins that we all have in our body, including the stomach and the intestine, have the property of reducing the amount of gastric secretion. They reduce the total volume of secretion as well as the acidity that is formed by the gastric glands. When we realized that, it occurred to us it might be a way to cure ulcers, because it has always been assumed and almost demonstrated that if there is no acid in the stomach, then there is no ulcer. It is very, very rare to find a patient who happens not to have acid in his stomach who will have an ulcer. It's a rarity. An article is written when this happens. So if, indeed, the prostaglandins inhibit gastric secretion, they should inhibit ulcer formation. Animal experiments proved that.

Indeed, when we administer prostaglandins to animals, and then try to produce ulcers, or if they have ulcers and we give prostaglandins, the ulcers disappear.

So we have two facts that have been uncovered. First they are antisecretory for the stomach, and second, they are antiulcer.

When this was found, it came the time to do some clinical testing in ulcer patients, to see if, indeed, we could reproduce in humans what we could obtain so easily in animals. We went to Europe to do some clinical studies in four countries, in which we used one of our most active prostaglandins, and when the study was completed, 18 months later, then we decoded everything and, indeed, the results were encouraging. The patients who had an ulcer at the beginning of treatment, many of them were cured in 14 days.

I must say that even if we give nothing to a patient for ulcers, there is a tendency to heal. But then it comes back after a few months or a year. So when we compared the healing after 14 days in the placebo treated with the prostaglandin treated, there was a big difference in favor of the prostaglandins, twice as fast healing. In 20 days the same ratio, the same difference, was also observed. We, then had been able to establish that not only in animals but also in humans certain prostaglandins were antiulcer.

More recently another property was also found for these prostaglandins which was called cytoprotection, cyto being the Greek word for cells, and protection being what we all know it is.

Very briefly, cytoprotection was discovered by if taking laboratory animals like rats and giving them orally certain irritants that will damage the stomach, such as pure alcohol or a strong acid, a strong base, a hypertonic solution, bile salts, things that are really very bad for the stomach, and kill inside the cells. Then we kill the

animals and look at the stomach, see that the cells have been destroyed.

In other animals, if we have given small amounts of prostaglandin just a few minutes before these very damaging agents, nothing happens. We have a total protection of the stomach. This has been extended to the intestine also, where this cytoprotective property exists as well.

Now, the interest in this newly discovered property is that minute quantities of the prostaglandins suffice to afford this protection. We don't need to give doses that would inhibit gastric secretion. In fact, the doses are about one-hundredth of the antisecretory doses that will protect completely either the stomach or the intestine.

This is what we are working on now. We are trying to find the minimal effective dose in humans that will protect the lining of the stomach and the intestine without producing any other effects that for an ulcer patient we don't wish to have.

I would point out or iterate that these substances are not foreign to the body. We all have them and they are natural substances. I think their applications are likely to cover a large number of important diseases of the digestive tract, from esophagitis to gastric ulcers, duodenal ulcers, gastritis, and several diseases known under the name of inflammatory bowel disease, such as Chohn's disease and ulcerative colitis. So we are quite excited about these new developments and are putting a lot of effort in that. Thank you.

[The prepared statement of Dr. Robert follows:]

THE PROSTAGLANDINS

André Robert

Department of Experimental Biology
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My name is André Robert. I have worked at The Upjohn Company for the past 26 years as a research scientist. Prior to coming to Upjohn, I obtained a medical degree from the University of Montreal Medical School, and then a Ph.D. degree from the Institute of Experimental Medicine and Surgery, also in Montreal. Let me say first that I appreciate this opportunity of appearing here. I hope that my testimony will be helpful.

I am particularly pleased to discuss research on prostaglandins, an area in which I have been working for several years. Although Upjohn scientists are studying many aspects of prostaglandins, in particular their biological properties and potential uses in a variety of important medical areas, I have chosen to concentrate on their effects on the digestive system, since this has been the focus of my own research.

The prostaglandins are a family of natural compounds believed to be present in every cell and tissue of the body. They consist of a skeleton of hydroxy fatty acids. Approximately 20 [illegible] have been isolated from mammalian tissues and many more have been synthesized in the laboratory.

Prostaglandins [illegible] biological activities. For [illegible] while others are

vasodilators, some prevent platelet aggregation while others favor it, certain PG are bronchoconstrictors and others bronchodilators. These various effects are due to slight changes in the prostaglandin molecule.

These substances were first discovered in the mid-1930's in seminal fluid by von Euler in Sweden and Goldblatt in England. It was not, however, until the late 1950's that Bergström and his coworkers isolated prostaglandins in pure form and a few years later determined their chemical structure. In the mid-1960's, scientists at Upjohn devised processes to obtain large quantities of these compounds, first by biosynthesis (formation of prostaglandins from incubated mammalian tissues) and later by total chemical synthesis. These developments not only increased the supplies of some of the natural PGs, but also led to the synthesis of new PGs, called PG analogs. These were prepared for the purposes of increasing the potency, allowing activity by the oral route, and obtaining PG that could affect more specifically only one organ or system at the time.

Gastric Secretion

Several prostaglandins inhibit gastric secretion in animals as well as in humans. This effect is observed after parenteral (subcutaneous, intramuscular, intraveneous) as well as oral administration. The anti-secretory effect produced by some prostaglandin analogs lasts several hours.

Ulcer Formation and Ulcer Healing

A variety of prostaglandins was found to inhibit formation of gastric and duodenal ulcers produced experimentally in animals.

This includes ulcers caused by acid hypersecretion and by severe stress such as exposure to cold, forced running, severe infections.

Certain methyl analogs of PGE_2 promote the healing of gastric and duodenal ulcers in man. Using one of our most promising PG analogues, arbaprostil, we recently conducted a multicenter clinical study in Europe. It was aimed at determining for the first time whether such a PG analog would cure duodenal ulcers. The results, obtained in 173 patients from four countries, showed that indeed arbaprostil accelerates the healing rate of duodenal ulcer. The effect was as marked as that obtained with cimetidine. Studies are currently under way to find out whether maintenance treatment with a prostaglandin would postpone or prevent recurrence of ulcers. We also have reports that PGE_2, a prostaglandin that does not reduce gastric secretion when given orally, markedly accelerates the healing rate of duodenal ulcers.

In pursuing our research with arbaprostil, we were able to identify certain side effects in some individuals. When administered at high doses, arbaprostil tends to produce some diarrhea and mild uterotonicity. We are concentrating our efforts in finding the minimum effective dose that heals ulcers without producing these undesirable effects. Results accumulated so far in that direction are very encouraging.

It may be well at this time to mention that development of an anti-ulcer drug has its particular problems. First, it is in the nature of ulcer disease to often heal spontaneously in one to two months, although it usually recurs within a year. Second,

objective assessment of healing requires frequent endoscopic examination, a procedure not always accepted by the patients. Third, patients considered for a clinical study have a variable history with regard to the duration of their disease (months or years), number of prior episodes, and initial size of the ulcer. As a result, a large number of patients are required for each study in order to arrive at significant conclusions. It is not uncommon for one such clinical study to take two years before being completed.

Cytoprotection

A new property for prostaglandins, called "cytoprotection," was discovered recently, and is shared by arbaprostil. It was first demonstrated in animals. Several PGs protect the lining of the stomach and the intestine from severe damage produced by agents such as alcohol, a strong acid or a strong base. What is remarkable in these studies is that minute quantities of PG are sufficient to prevent the damage.

Since such small quantities have no effect on gastric secretion, it was concluded that the antisecretory and the cytoprotective properties are independent of one another. Other studies showed that the gastric intolerance of nonsteroidal antiinflammatory compounds such as aspirin can be adequately prevented by treatment with "cytoprotective" prostaglandins. Thus, both in animals and in humans, gastric bleeding and gastric erosions caused by aspirin or indomethacin, drugs commonly used for the treatment of arthritis, were prevented by minute doses of PGE_2, a natural prostaglandin.

The fact that very small doses protect the gastrointestinal mucosa suggests that a variety of gastrointestinal diseases could

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be treated with doses of PG that are without clinically significant side effects. At the moment, we believe that such diseases would include esophagitis, gastritis, gastric and duodenal ulcers, and various forms of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Some authorities believe that the chronic inflammation and mucosal irritation characteristic of these diseases may lead to precancerous lesions. One can only speculate at this time on the possible beneficial role of prostaglandins in such situations.

Impact of Cytoprotection

Gastrointestinal diseases are among the most frequent in the general population. Because of their tendency of being chronic, their economic impact in terms of hospital costs, reduction of industrial productivity, reduced income due to lack of work, amounts to billions of dollars every year. The significance of digestive diseases was recently highlighted in the findings of the National Commission on Digestive Diseases, established by the Congress on October 19, 1976. The 26-member Commission found that in the year 1975, digestive diseases in the United States accounted for:

-10 percent of total days of illness among adults.

-27 percent of all admissions in general hospitals and Veterans Administration hospitals combined.

-25 percent of all surgical operations.

-Direct medical costs of $8.1 billion, with a projection of $17 billion for 1978.

-An economic loss of $23.4 billion, with a projection of $35 billion for 1978.

The current treatment for most of the digestive diseases is at present very unsatisfactory. In fact, there is no treatment

for Crohn's disease except surgery, there is no treatment for gastritis, the treatment of esophagitis and gastric ulcer is often unsuccessful. In the case of ulcerative colitis, drugs like sulfasalazine and steroids are used with moderate success. In an important percentage of patients, the only remaining treatment after repeated recurrences is surgical removal of large segments of the colon. The treatment of duodenal ulcer has been improved in recent years due to the advent of cimetidine, although many investigators worry about the long-term effects of a drug that has to be absorbed systemically and therefore be distributed throughout the body in order to reduce gastric secretion and favor ulcer healing.

An interesting property of prostaglandins, in addition to the low doses required, is that they act on the gastrointestinal mucosa both locally and systemically. Therefore, they may not necessarily need to be absorbed through the body in order to affect digestive diseases. By taking them orally, one could achieve the equivalent of a "topical" effect since by this route these agents come first in contact with the linings of the stomach and the intestine.

Conclusions

Prostaglandins are likely to become some of the most beneficial therapeutic substances for several ailments, especially for the treatment of digestive diseases. Their potential use is the direct result of more than 40 years of basic research. Experimental evidence obtained especially during the last seven years shows that prostaglandins maintain cellular integrity of the gastrointestinal tract in spite of the presence within its lumen of noxious agents, including bacteria and their toxins. They appear to play a role

in the natural defense of the tissues of the gastrointestinal tract. On the basis of these data, we hope to be able to expand the clinical study of these substances in a variety of diseases, so that patients can benefit from their use. A major effort is devoted to the development of these very promising compounds. We are very enthusiastic about the outcome of this research. The fact that prostaglandins are natural substances makes their clinical application particularly appealing.

I wish to thank you again for this invitation to come to this hearing, and would be happy to answer any questions you may have.

Mr. SCHEUER. Thank you.

Let's now hear from Mr. Faust.

Dr. FAUST. My name is Dr. Richard Faust and I am director of research planning and development for Hoffmann-LaRoche. In the interest of time, I will try to summarize briefly the statement which I submitted to you. But before doing that, I would like to just make a couple of preliminary comments.

First of all, I would like to say that, as a member of industry, I heartily endorse the comments I heard this afternoon by Dr. McMahon. It is my view that if we were to implement the various suggestions he made, we could cut at least 3 years off the drug development process, perhaps even more. That, coupled with the patent restoration legislation which we hope will pass, would provide I think significant incentives for the pharmaceutical industry.

Another preliminary comment has to do with the comment that Dr. Goodwin made. I would like to assure Dr. Goodwin, even though he's not here, and you, the committee members, that Roche has no contact with God. [Laughter.] However, we are working in many of the same areas that Dr. Goodwin described to you. Our Roche Institute of Molecular Biology, which has nearly 200 research scientists and supportive staff working in the area of molecular biology, does encompass some of these receptor mechanisms which you heard Dr. Goodwin and Dr. Bloom describe.

With regard to the topic of prostaglandins, I mention in my written testimony the arachidonic acid metabolic pathway, which I will not take the time to explain here, except to say that through this mechanism—and prostaglandins represents one segment of this complex metabolic pathway—we can develop new drugs which will influence bronchial disease, cardiovascular disorders, gastro-intestinal disorders, and as Dr. Robert just mentioned, a whole host of inflammatory conditions.

We have in our research laboratories a compound that is being tested in ulcer therapy which is in phase II clinical trial. We have several others that do look promising in other therapeutic areas. For example, in cardiovascular disease we have an analog that in a single dose in animals will reduce blood pressure for as long as 24 hours. We have several other leads that we hope will prove valuable in treating allergic bronchial asthma. So we have a number of interesting leads in the research pipeline in this arachidonic acid cascade system.

I would like to spend what time we have to talk a little bit about the relationship of what we're doing to the research process. Congressman Gore mentioned he intends to study the research process and how it is carried out. I would like to suggest several points with regard to the work we're doing in the arachidonic acid cascade which relate to this complex process.

First of all, a research effort of this magnitude requires a critical mass of many scientists, not only chemists and biologists but clinicians and pharmacists and statisticians and a whole group of other supportive scientists and skilled personnel. It is within the pharmaceutical industry where we find this sort of teamwork. I would imagine this accounts in part for the fact that it is from the private pharmaceutical sector that most of our drugs have evolved since 1940.

Second, the impact of inflation on the research process is considerable. In my written testimony I talked about the very low levels of drugs that are being used today in microgram quantities, such as with the anti-ulcer drug that I mentioned.

I can tell you that the sophisticated instrumentation that we're using to detect nanogram quantities of drugs in the blood system and in other body tissues, that these instruments do, indeed, increase in cost at an average rate of about 20 percent per year terms of cost. It is estimated that the impact of inflation on the research process is as high as 15, and I've seen other estimates as high as 20 percent.

The third point I would like to mention is one which I feel very strongly about, and that is that in the development of pharmaceutical products and in our work on this arachidonic acid metabolic system the pharmaceutical industry does generate new knowledge which feeds the storehouse of scientific information that is available to everyone. There are innumerable examples one could mention of how in the course of developing a new pharmaceutical product a company does contribute to this knowledge. It's a contribution which I think is oftentimes overlooked.

One other point. If we recognize that the drug development process now ranges from 7 to 10 to 13 years, depending on the drug substance, that means that for any new pharmaceutical to emerge during the decade of the eighties, if we are to have a breakthrough in the eighties, that compound must be in the development stream, in the development process, today.

One last point. I think that the pharmaceutical industry, as you have heard from Dr. McMahon and others, does have the capability of alleviating many crippling diseases in the future. We do need, however, to preserve the incentives to continue these large research investments so that we can be productive and so the industry can contribute as a national resource.

Oftentimes at these hearings and in other discussions we talk about those who are the stakeholders in this process, and whether we're talking about the geriatric population or the orphan drug population or other groups, it occurs to me that there is frequently one strong stakeholder that is never mentioned. That is the stakeholder represented by your children's children and their children; in other words, future generations. I think we have to preserve the incentives within the private sector to maintain and develop basic exploratory research programs which are now under pressure in many pharmaceutical firms. We need to preserve this investment in basic research so that we will have the drugs of the future, which as you know sometimes take as long as 15 or 20 years from the time of the original research until the final product emanates from the laboratory.

With those brief comments, gentlemen, I will conclude. Thank you.

[The prepared statement of Dr. Faust follows:]

STATEMENT OF RICHARD E. FAUST, PH. D.

My name is Richard E. Faust, Ph.D. I am Director of Research Planning and Development for Hoffmann-La Roche Inc., one of the largest research-oriented health care companies in the United States. I am pleased to have the opportunity to share with you some of the exploratory research we have underway at Hoffmann-La Roche in the area of prostaglandins and related substances.

Prostaglandins represent one group of a related set of substances which are part of a metabolic pathway in the body known as the arachidonic acid cascade. This metabolic pathway may be affected at various points by agents which inhibit certain enzymatic reactions or which block or enhance various components of this pathway resulting in pharmacological actions having a positive effect in various diseases of the lungs, gastrointestinal tract, the cardiovascular system, and in inflammatory conditions. Having recognized the importance of early findings in this field, we have established research programs seeking to find compounds that affect one or more steps in this metabolic pathway. Through this, we hope to provide new therapeutic approaches to several disease states affecting several body organ systems. A number of possibilities exist for developing significant new drugs by modulating this metabolic system.

For example, various approaches are being pursued in our laboratories to find compounds which inhibit a substance labeled SRS-A (slow releasing substance of anaphylaxis), which causes bronchoconstriction. There are

several points in the arachidonic acid metabolic pathways which may be influenced to bring this about. We are now examining interesting leads which could provide a drug that would be valuable in treating allergic bronchial asthma.

In the cardiovascular research area, we have noted that certain analogues of the naturally occurring prostaglandins have long-lasting antihypertensive activity. Extensive structure-activity studies are being pursued in an effort to achieve potency and pharmacologic specificity. Some analogues are available which reduce blood pressure in animals for as long as 24 hours after a single dose. Different analogues show promise in other cardiovascular areas such as thrombosis, platelet aggregation, and ischemic heart disease.

Modulation of arachidonic acid metabolic pathways may provide an approach to the treatment of a variety of intestinal diseases. We currently have in clinical trial a compound that could have important anti-ulcer properties. Not only does it inhibit acid secretion in the stomach, but it also appears to inhibit pepsin secretion and enhance mucoprotein synthesis which would provide additional protection to the gastric and intestinal wall.

In summary, we feel that there are important opportunities for the development of novel and useful drugs by the selective modulation of arachidonic acid metabolism. Since this area of drug development is relatively new, there are many possibilities and we intend to continue our search to find agents that will provide important new therapies.

Work in areas such as the arachidonic acid cascade is illustrative of several trends today in the complex drug discovery and development process. First, the process involves the interaction of a critical mass of many scientists who work together closely to generate new pharmaceuticals. For example, when SRS-A was first identified, researchers skilled in fatty acid chemistry were called upon to synthesize the substance and make it available for study. This interaction between biological and chemical specialists is vital in the biomedical discovery process and such close working teams augmented by clinicians, pharmacists, statisticians, and others are found primarily in pharmaceutical firms. The yields from this teamwork and research efficiency are reflected in the fact that the vast majority of the new chemical entities introduced in this country from 1940 to 1978 came from the private pharmaceutical industry.

Second, many new drugs are active at extremely low dose levels so that measurement and detection become most challenging and require costly, sophisticated instrumentation. The fact that we now have instruments and techniques which can detect nanogram and even picogram quantities of drug substance in tissues such as blood allows us to give more careful attention to drug distribution, drug metabolism, and pharmacokinetic profiles. For example, with the anti-ulcer lead I previously mentioned, the dose is measured in micrograms. In order to study its distribution and metabolic pathway in human subjects, we use complex gas chromatographic and mass spectrometry techniques capable of detecting nanogram amounts of the drug. A nanogram is one billionth of a gram. Using an analogy to place these quantities in perspective, if one nanogram equals one inch, then a pound of such a substance would stretch over seven million miles.

Third, work in this area of finding agents affecting arachidonic acid metabolism is an example of the important role of drug development in gaining new knowledge and broadening the frontiers of basic science. As we search for new drug leads in this area, we are generating new facts and information concerning basic biochemical mechanisms in the human body. An often overlooked contribution of our industry is the storehouse of biomedical scientific knowledge that occurs during and as a result of drug development programs. For example, the finding that indomethacin and certain other anti-inflammatory agents block prostaglandin synthesis has allowed the use of these drugs as tools to study the role of prostaglandins in the body.

In conclusion, it is well recognized that the drug development cycle is a lengthy process which now averages 7 to 13 years. This means that for a new therapy to emerge from our laboratories and be approved for patient use during the decade of the 80's, we must have already identified the agent and have it under active development. Therefore, we must recognize that a "breakthrough" is really based on the accumulation of scientific data from many groups and the result of a long development program.

While there is no doubt that the research and development process is complex, expensive, and financially risky, there is also no doubt that its rewards to society are great. Reflecting upon the past several decades, the contributions of the pharmaceutical industry's research and development efforts have been manyfold -- the prevention, treatment, and

cure of many diseases; the enhancement of the quality of human lives; the containment of overall health care costs -- in addition to its contributions to the national economy.

We believe that the pharmaceutical industry possesses the capability of alleviating many crippling diseases in the future. The challenge before us is to preserve the incentives for research and development investments and further enhance pharmaceutical industry research activity in recognition of its value as a vital national resource. We are encouraged by the positive interest of Congress, the Administration, and the public at large in our research activities, for we believe that innovation and discovery should be our common goal and actively supported by us all. You may be certain that we at Roche shall do all we can to make these potential new products which I have mentioned here today available as rapidly as possible.

Thank you for this opportunity to be a part of your examination of this important subject. I hope these few brief remarks have been helpful.

Mr. GORE. Thank you very much, doctor.

Dr. Robert, how soon do you anticipate that prostaglandins will be used in the treatment of gastric disorders here in the U.S. marketplace?

Dr. ROBERT. This has to be a guess. We're talking of years. Whether it is 5 or more years, it is difficult to tell. We need to accumulate enough clinical data to make a case for an NDA.

Mr. GORE. Are there problems that are particular to prostaglandins that you have identified at FDA?

Dr. ROBERT. There were two problems that came up in the course of clinical trials in the United States. One, the first one was uncovered in early 1977. It so happened that patients were given one of our prostaglandins, and when the treatment stopped, they did not resume secreting acid in their stomach as they should have. We immediately stopped clinical testing because it at first appeared to be due to the drug that was given. After a couple of months, however, it was found that even patients who had never received any prostaglandins also, some of them, were not secreting acid at all. Other cases turned up in Boston who had never been exposed.

In summary, this was ascribed to a virus infection, totally unrelated to the treatment given. So it was coincidental. But we stopped and the FDA was notified immediately. They told us also not to continue until this was resolved.

But then a second problem turned up. The FDA was reviewing all the data that we had sent 2 years earlier and found that in the stomach of animals that were treated, some of the cells were more numerous than in the controlled animals. They expressed some concern that this might be detrimental and told us not to continue clinical testing until we had explored this problem and came to an explanation.

Well, it took a very long time to do; after discussions—we sent our slides to FDA for them to examine. Our pathologists were of the opinion that it had no deleterious effect at all, and outside pathologists and consultants agreed with us. But the FDA scientists thought that this was serious enough to not continue resuming the studies.

There was an honest difference of opinion here. Since we could not resolve this question rapidly, then we went abroad, submitted the same data to both investigators and government agencies of four foreign countries, and they all allowed us to resume clinical testing there. This was the study I was referring to when I mentioned the good results that were obtained.

Mr. GORE. Dr. Faust, you mentioned in your statement that prostaglandins have shown promise in treating diseases of the lungs, the gastrointestinal tract, cardiovascular system, and inflammatory conditions.

Which of these areas is now receiving the most concentrated research effort?

Dr. FAUST. Within our firm, we are working in all areas. But the one area that is receiving the most concentrated attention is the gastrointestinal tract where we have several important leads. One, as I mentioned, is in clinical trial now. The other leads have not moved into man as yet, and we are in the process of trying to select the better candidates to go into clinical trial.

Mr. GORE. Do you think that is true of your competitors as well, from as much as you can glean of what's going on in the field generally?

Dr. FAUST. I really can't address the nature of the work of the competitive firms. Perhaps Dr. Robert would know a little more than I do about this competitive——

Dr. ROBERT. If you will tell me your leads, I will tell you my leads. [Laughter.]

Mr. GORE. You know, your testimony is immune here before this hearing. [Laughter.]

You talked, Dr. Faust, about the challenge—and I quote—"to preserve the incentives for research and development investments, and further enhance pharmaceutical industry research activity." I don't think anybody disagrees with you on that point. Certainly I do not.

You mentioned patent restoration. That is proceeding in another committee. Are there any particular changes that you would recommend that relate specifically to prostaglandins?

Dr. FAUST. I don't place the prostaglandins in any special category in terms of research. I think they would offer the same challenges as our other research activities in other areas. There is nothing special, I would say, about that research field.

Mr. GORE. Do you think they're a likely candidate for priority treatment at FDA?

Dr. FAUST. Yes; I do. I think that the nature of the research in this area is providing so many interesting and exciting leads that I would imagine there would be several of these leads emerging which would warrant either a 1A or 1B classification at the FDA.

Mr. GORE. Well, I would like to say for the record that, as one Member of Congress who has looked at the FDA fairly closely, I certainly support the trend toward prioritization and would like to see the FDA take a close look at prostaglandins and cardiac drugs mentioned here earlier, the development of neuropsychopharmacology, the new vaccines, and other areas where we can get a huge return for the public, and take those areas on a priority basis through the approval process. Maybe that is one way to start quickly to remedy the problems you have identified, without risking the drastic change of deregulation of FDA that has been discussed.

I sometimes think we react like a pendulum too often in this country, swinging from one extreme to the other. I have been getting the impression during these hearings that what's really needed here is some fine tuning. Prioritization is one such fine tuning element. A couple of other specific recommendations were made earlier, and I referred to them at an earlier point in the testimony.

I respect your views on the more drastic remedies that Dr. McMahon discussed earlier. But maybe we can agree at least on some of these fine tuning measures that will give us a payoff relatively quickly.

Dr. FAUST. May I comment on this prioritization approach?

Mr. GORE. Surely.

Dr. FAUST. It is my understanding that approximately 15 percent of the compounds that are being evaluated at the FDA have been

put into the 1A or 1B category. I would hope this would not mean that the other 85 percent which do, indeed, represent valuable therapies, that these would be handled in an unprioritized way, in such a way that the approval time becomes longer. I would hope that we can accelerate both the priority and nonpriority compounds.

Mr. GORE. I would certainly share that hope. We both understand that that's a possibility when you're talking about prioritization. I hope that that can be avoided.

In studying the research and development process and the approval process, I hope that we can identify changes within FDA that could be made to speed up the approval for all applications across the board. I think we need to look at the incentives that people in FDA now have and why there are pressures on individuals working for FDA to always push in one direction. I think some of them are quite understandable and we don't want to remove all those incentives, but we want to look at them and see if we can fine tune the process and make it work better. I think that we can if we take a good, hard look at it, and if we have the kind of cooperation and sharing of perspectives that we've had during this hearing, I feel real hopeful about the outcome.

I would like to thank you both for your testimony here today.

Thank you, Mr. Chairman.

Mr. SCHEUER. Thank you, Congressman Gore.

The time is late, and we have imposed on your patience long enough.

I am going to ask one question of both of you. Dr. Faust, you mentioned you agreed with Dr. McMahon in his recommendations for change. It is my personal view that we need more than establishing priorities for FDA, priorities which they would apply to their already cumbersome and archaic system. I believe we need basic changes in that system of drug approval along the lines that Dr. McMahon recommended.

I would like to ask the two of you, has the regulatory process unduly and unnecessarily impeded the development of prostaglandins, your area of specialty, and if so, what recommendations do you have specifically for improving and accelerating the process of new drug approval?

Dr. ROBERT. I cited two examples, one in particular, where we—that is we, collectively, the scientists at Upjohn, and our consultants—felt that the FDA was not justified in not allowing further clinical testing in the United States. This delayed us by 2 years, exactly 2 years.

This is a difficult example, because there I think there was an honest difference of opinion. It was not due to certain regulations. It was a dialog between their scientists and ourselves and consultants from the outside.

There was a 2-to-1 vote, so to speak——

Mr. SCHEUER. The time is getting short. Can you just give us recommendations, if you have any, as to how this regulatory process can be improved so as to approve drugs in a far shorter timeframe and require less than the $50 or $75 million that Hoffmann-La-Roche and other companies are spending? Just recommendations on how we can improve the process.

Dr. ROBERT. Reduce the paperwork by 80 percent. Reduce——

Mr. SCHEUER. Excuse me, Dr. Robert. I'm going to ask you, perhaps before you go to France, to give us some suggestions as to how we can reduce the paperwork by 80 percent, some specific suggestions.

Dr. ROBERT. I wish Dr. McMahon had not been here before because we're all going to repeat some of his suggestions that do not sound so original.

Mr. SCHEUER. Let me amend my question. Is there anything you would say in addition to what Dr. McMahon has said?

Dr. ROBERT. I don't think so.

Mr. SCHEUER. You think he pretty well summed it up.

Dr. ROBERT. Yes.

Mr. SCHEUER. How about you, Dr. Faust?

Dr. FAUST. I think his suggestions were very much on target and represent, I think, most of the feeling in industrial circles as to how we can speed up this process.

I think the paperwork, the paper blizzard that we generate, makes it a problem for us and it also makes it a problem for the FDA. I think one point that came out today I think we would agree with is that the FDA has a real problem in handling all the paper that we send down there, so that by decreasing this paperwork, it would aid not only us but also facilitate the approval process in terms of the people working at FDA.

Dr. ROBERT. If I were the head of the FDA and was seeing the tons of paper and documents that have come on their loading dock there, I would be discouraged because I would know that almost no staff cannot only read this, but especially analyze this properly. It's an impossibility.

Mr. SCHEUER. Of course, it's far beyond their capability, and in a time of constraints in our economy and our Government, they're not going to get more staff; they're going to get less staff. While at the time you folks are leading us into this incredible drug revolution, they're going to have to make do and try and cope with the new process, the new drugs that you're shoving at them, with a grossly inadequate staff and an even more grossly inadequate system.

Dr. ROBERT. If I may address one last word here, sometimes it comes to the point that it is discouraging to do further research, because we will, if we work hard, we will discover new chemicals for which we find applications by experimentation in animals, and then we know they will be put on the shelf there and stay there for years.

Mr. SCHEUER. Thank you very much.

Mr. Carney.

Mr. CARNEY. Mr. Chairman, I would just like to say that Dr. Robert's last comment was perhaps worthwhile waiting for all day, where you just said to this committee that you are perhaps discouraged from doing further research in the field of pharmacology because of the problems that we're beset with.

I would just like to finish by saying—and I'm sure under the leadership of our chairmen of both subcommittees, Mr. Gore and Mr. Scheuer—that we will take the testimony that was given today by all witnesses—and I would say when you have Members of the

U.S. Congress at 6:30 in the evening still standing here and wishing there was more time to listen, that testimony was worthwhile listening to. You have done a great job and I believe if we do our job you will have done a service to the people who we're trying to serve, the people of our Nation. I thank you and I thank all the panelists who are still here, and those who unfortunately had to leave because of their schedules. We have a job to do, and I believe with your help and direction we can do that.

In a final statement, I would like to ask one question off the record for Dr. Faust.

[Discussion off the record.]

Mr. SCHEUER. Congresswoman Schneider.

Mrs. SCHNEIDER. I have just a few brief questions for Dr. Faust that would add evidence to the argument being put forward here today insofar as reducing paperwork.

To what extent are prostaglandins used in routine medical treatment in Europe today, currently?

Dr. FAUST. I don't believe that any of the prostaglandins are widely used in Europe. I——

Mrs. SCHNEIDER. Anywhere in the world?

Dr. FAUST. I don't believe so in large scale. They are used in animal health preparations on a rather limited scale.

I believe Dr. Robert might be able to comment a little further on that.

Mrs. SCHNEIDER. Are you in agreement with that?

Dr. ROBERT. Yes, I agree with Dr. Faust, and there is a reason for that. It is that the mass production of very active prostaglandins has been from the United States. We went to Europe and then the Europeans are waiting for these same results to approve these prostaglandins for clinical use.

Mrs. SCHNEIDER. This is almost a reversal of situations, because it appears that so often other countries are waiting for the United States to pick up on their particular drugs.

I wonder if you could give some examples of drugs available overseas that were delayed in becoming available here? Dr. Faust?

Dr. FAUST. Drugs available overseas that were delayed——

Mrs. SCHNEIDER. Yes, that have been delayed because of our own regulatory paperwork and bureaucratic system.

Dr. FAUST. I would just refer you to the enormous work that has been done by Dr. Lasagne and Dr. Wardell at the University of Rochester where they have tabulated a great deal of research and enumerated many drugs, mainly those in the cardiovascular area, those in the broncho-pulmonary area, and those in the gastrointestinal area. Those seem to be the three major therapeutic categories where there have been significant delays.

Mrs. SCHNEIDER. Is there any evidence that this drug lag has resulted in a definite decline in innovation among U.S. drug firms?

Dr. FAUST. I certainly think so. I think the fact that we cannot match the approval process of the foreign firms does indeed have a negative impact on the incentives for innovation.

Mrs. SCHNEIDER. Are there many U.S. firms that are taking U.S. capital abroad and investing it there for research, development, and marketing of drugs because it's easier to get drugs moving along outside of the United States?

Dr. FAUST. Yes; in 1962, as I recall, the research investments for the major American firms in overseas research, amounted to about 5 percent. This figure has steadily increased until this year I believe it's estimated that between 19 and 20 percent of the total research budgets of these American firms are invested in overseas research efforts.

Mrs. SCHNEIDER. Just one final question.

Can you give me an estimate of the approximate cost of bringing a new chemical entity into the marketplace?

Dr. FAUST. That can be answered in several ways, depending on whether one accounts for the time value of money, leads that have been lost along the way and so on. But again, the group at the University of Rochester has done some excellent work in quantifying this information and I believe the latest estimate is approximately $70 million. This is an increase, by the way, from about $6 to $7 million back in 1962.

Mrs. SCHNEIDER. Overwhelming.

Well, I too echo Mr. Carney and the chairmen's comments in appreciation of your thoroughness. Thank you very much.

Thank you, Mr. Chairman.

Mr. SCHEUER. Thank you, Mrs. Schneider.

One last question before I turn the Chair back to Congressman Gore.

One of you said a few minutes ago—I jotted down the note but I forgot to jot down the author of the statement—that we went to four countries in Europe. I believe that was you, Dr. Robert. Why did you go to Europe instead of proceeding with that research here?

Dr. ROBERT. We wanted to stay in the United States. It is much easier, more practical, to continue to work with investigators we know very well. We can call them on the phone. There is no time difference, where the maximum is only 3 hours. We can take a plane and be there in 2 hours.

Because of this difference of opinion between FDA scientists, ourselves, and our consultants, as to the significance of certain data we had obtained, we were then banned from continue research in humans in the United States. We had no choice.

Mr. SCHEUER. What difference did it make?

Dr. ROBERT. In rats and dogs given the prostaglandins we were interested in, there were more cells in the stomach than in the control animals not receiving prostaglandins. We interpreted that as being a beneficial effect, that it may be one way that the stomach can protect itself from becoming ulcerated.

The FDA scientists took the view that this might be a form of tumor developing and they were concerned about it. We were very concerned, also, but we did additional data, studies, showing that this change was totally reversible when we stopped the treatment, and No. 2, that this kind of change is just the opposite of what takes place when cancer is going to take place. Just the opposite. So there was a disagreement.

We went to four different countries with the same data—Belguim, Holland, France, and Poland was the fourth one.

Mr. SCHEUER. What kind of environment did you find behind the Iron Curtain?

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Dr. ROBERT. It was excellent. The reason we went there was that I knew several investigators in Poland who had published very much. I see them at meetings.

You see, there is one thing we have to remember. When we say that we go abroad and should we use foreign data, those are not data and investigators that come out of the blue. We know them. They are my peers. I see them at meetings, at international meetings. They come here, I go there. I read their publications, they read mine. So they are already established investigators, very reliable. We visited them before starting the study. We saw their facilities and, in addition to knowing them and their reputation, we were satisfied. The results confirmed the faith we had in them. They were very good.

Mr. GORE. Mr. Chairman, I would like to thank our witnesses and extend that expression of thanks to all of the witnesses that we have had throughout the day, and express my appreciation to you for initiating this joint hearing. I think it has been most enlightening, quite useful, and I sincerely hope that as a result of the testimony we have received today we can come up with sensible recommendations that will improve the process at FDA and make it possible for Americans to receive the benefits of these breakthrough drugs of the eighties quicker than they otherwise would.

I just appreciated the chance to participate in these hearings.

The hearing is adjourned.

[Whereupon, at 6:35 p.m., the joint subcommittees were adjourned.]

APPENDIX

TULANE UNIVERSITY SCHOOL OF MEDICINE

Department of Medicine
1430 Tulane Avenue
NEW ORLEANS, LA. 70112
588-5511

Therapeutics Section

May 1, 1981

The Honorable James H. Scheuer
Chairman, Committee on Science and Technology
U. S. House of Representatives
Suite 2321, Raybourn Office Building
Washington, D.C. 20515

Dear Congressman Scheuer:

During my testimony for your committee on Monday, April 27, I was asked about my personal experiences in obtaining Verapamil for my personal emergency use because of my inability to be adequately controlled with standard old drugs.

Verapamil is the first of a series of new calcium-blocking agents which drugs aid cardiac arrhythmias, angina pectoris (coronary chest pain) and perhaps even hypertension. Verapamil is on the market in over 100 countries in Europe, many of them for the past 18 years. It is still not available in the United States except as an emergency or compassionate drug, and requiring therefore a great deal of paperwork for the Food and Drug Administration. In my judgement, and certainly in most cardiologists' judgement, this class of drug should be available for the American heart patients.

I hadn't intended to get into a discussion of Verapamil at the hearings, but since the matter came up, I did explain to you my difficulties and resentment for having been given a large stack of paperwork to fill out and a great deal of red tape before I could use it myself. You asked me to send you a copy of this paperwork as further documentation of the FDA drug lag and the nit-picking requirements of the current operating procedure imposed by FDA regulations, codes and guidelines. I enclose copies of this material as you requested. When an important new class of drugs which has been on the market for over 18 years in some countries and is on the market of virtually every country in the world, including Russia and China, is not available for American patients with heart disease at this late date, there is certainly something wrong with our system!

I fully support your efforts to improve the over-regulation imposed by FDA.

Sincerely yours,

F. Gilbert McMahon, M.D.
Clinical Professor of Medicine

FGMcM:fj

INFORMED CONSENT 3/24/81

Emergency (Compassionate) Use of Isoptin When Patient Has Not Responded to, or Cannot Tolerate Conventional Therapeutic Agents

I understand that I have been asked to participate in this study which will involve my receiving the investigational drug Isoptin (verapamil), which has been shown be be effective as treatment for some abnormal heart rhythms and angina pectoris in many other countries for years.

I understand that I will not be allowed to participate in this study if I have been diagnosed as having heart block or heart failure (unless caused by rapid heart rate). Isoptin should not be used at the same time or immediately before or after a beta-blocking drug or disopyramide phosphate(Norpace). Isoptin should not be used when digitalis excess is suspected.

Numerous clinical trials reported in world literature suggest that verapamil is an effective and well-tolerated antianginal agent, and in the treatment of episodes of arrythmia it was reported to be effective. The most frequently reported side effects that have occurred include headache, dizziness, constipation, nausea and heart failure. The relationship of these to Isoptin was not known in some instances. Cataracts were noted in beagle dogs but have not been detected in humans, rats or baboons after treatment with Isoptin.

I understand that the drug will be administered by a board certified cardiologist after it has been determined that no other cardioactive drug has proven effective and my physician has decided that Isoptin may provide greater relief than conventional therapy and/or enhance the quality of my life.

This study will involve my receiving a dose of _____ to _____ mg of Isoptin. I will be examined by my physicians at least once a day if hospitalized, and as an outpatient at least once every two months, or more often if deemed necessary, to assess the effectivness of the drug. I will have eye examinations done if treatment exceeds 30 days.

I understand that my participation in this study is voluntary and that I may choose not to participate and this will in no way influence my treatment. Furthermore, I may withdraw whenever I might choose. The investigator may elect to terminate my participation in this study at any time he feels it would be in my best interests. If new information develops during the course of this research project pertaining to drug safety, such information will be given to me. If I have any questions concerning this study or this form, they will be answered to my satisfaction

I understand that if I should have any injury due to participating in this study, medical treatment shall be available through the investigator at no cost to me. Questions regarding the availability of such medical care and/or compensation can be directed to the sponsor through the physician conducting this study at any time. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available, however, in the event of such injury I understand that I have not waived any of my legal rights by signing this form.

I understand that the data obtained during this study will be treated confidentially by the investigator. I authorize release of information from this study to those agencies designated by the granting agency, Federal Drug Administration and/or the principal investigator.

I have read and understand the information stated above and I sign this consent form willingly.

SIGNATURE:_____ DATE_____

WITNESSED:_____ DATE_____

I am unable to read but this consent form has been read and explained to me;
by_____(name of reader). I understand the
information stated above and I willingly sign this form.

SIGNATURE:_____ DATE_____

WITNESSED:_____ DATE_____

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD • WHIPPANY, NEW JERSEY 07981

March 18, 1981

Re: ISOPTIN (verapamil HCl)
Emergency (compassionate) Use
Patient: FGM (M-57)
SC (M-30)

Jerome Ryan, M. D.
Professor of Medicine
1430 Tulane Avenue
New Orleans, Louisiana 70112

Dear Doctor Ryan:

ISOPTIN (verapamil hydrochloride) is not yet approved by the Food and Drug Administration (FDA) for use in the United States in other than approved clinical research programs under an Investigational New Drug (IND) application. However, this restriction may be waived in situations in which conventional therapy is ineffective in, or not tolerated by, a particular patient providing that therapy with ISOPTIN is considered in the patient's best interest. For such patients, we may provide supplies of ISOPTIN (5mg [2ml ampules] for intravenous use and/or 80 and 120 mg tablets for oral administration) to physicians/cardiologists for their use under certain conditions:

1. Under FDA regulations written informed consent must be obtained from the patient; the consent form must be retained in the patient's permanent hospital or office file.

2. The supplies of ISOPTIN sent to you in response to your request regarding a particular patient may be used only for that patient; they may not be retained or used for any other patient. All unused supplies of ISOPTIN are to be returned to Knoll Pharmaceutical Company.

3. Only physicians named on the FDA "Statement of Investigator" Form #15/3 described in item 7a below may dispense these supplies of ISOPTIN.

4. Patients on ISOPTIN therapy are to have periodic examinations, as described in the enclosed Protocol for Emergency (Compassionate) Use of ISOPTIN, at intervals of no more than 3 months. The results of these examinations are to be forwarded to Knoll Pharmaceutical Company on the

Follow-Up Evaluation Report (Item 7B) described below.

5. As suggested by FDA guidelines for all systemically absorbed drugs, a complete ophthalmologic examination should be obtained prior to the patient reaching 30 days on ISOPTIN whenever chronic therapy is anticipated. Follow-up examinations should be done at intervals specified in the enclosed Protocol for Emergency (Compassionate) Use of ISOPTIN. The results of these examinations are to be forwarded to Knoll Pharmaceutical Company.

6. Confidential documents to be reviewed and RETAINED by you:

   a. ISOPTIN Investigator's Brochure. This brochure describes the basic pharmacology and the worldwide clinical experience with ISOPTIN. We urge you and any co-prescribers of ISOPTIN to become thoroughly familiar with this information, paying particular attention to the contraindications to and precautions for the use of ISOPTIN.

   b. Protocol for Emergency (Compassionate) Use of ISOPTIN. This protocol describes the procedure for the intravenous and oral administration of ISOPTIN under the Emergency (Compassionate) Use Program. Please review this protocol thoroughly before administering ISOPTIN.

7. Preliminary Documentation to be Completed and Returned to Knoll Pharmaceutical Company Immediately:

   a. FDA "Statement of Investigator" Form #1573. Please complete and sign this form and attach a copy of your Curriculum Vitae including your Cardiology Board certification status/number. The drug will be released by Knoll to the physician/cardiologist signing this form, who will assume primary responsibility for the use of ISOPTIN in a given patient. Any co-prescribers of ISOPTIN must be named under Section f, on page 2 of the form, and copies of their Curricula Vitae attached as well. Only physicians whose names appear on this form are authorized to dispense ISOPTIN, to sign follow-up reports, and to request additional supplies of this drug.

   b. "Request for Emergency Use ISOPTIN Report." This form summarizes information on the patient to whom you intend to administer ISOPTIN. Please verify the accuracy of the information already on the form and add any further pertinent data.

   c. "Prescribers Statement." This statement is found on the last page of the Protocol for the Emergency (Compassionate) Use of ISUPTIN. Please complete, sign, and detach this

page and return it to Knoll (keep a copy for your files).

d. List of package Contents. To confirm that you have received all relevant information, please review and compare this list with the contents of this package. Then sign the form, indicating whether you have or have not received all the items listed on the form. Please identify any items not received.

THE DOCUMENTS INDICATED IN ITEMS a, b, c, AND d ABOVE ARE TO BE COMPLETED AS DESCRIBED AND RETURNED TO KNOLL IN THE POSTAGE PAID ENVELOPE PROVIDED IMMEDIATELY UPON RECEIPT OF THIS PACKAGE, PRIOR TO INITIATION OF ISOPTIN THERAPY.

8. a. ISOPTIN Case Report Form. This form is to be completed and returned to Knoll Pharmaceutical Company immediately after therapy with ISOPTIN has been initiated and a determination is made as to whether or not it will be continued. Return the original to Knoll; keep a duplicate in your files.

b. Follow-Up Re-evaluation Report. Complete and return this form at intervals of no more than 3 months. The entire form must be completed, signed and returned. Please note that only written requests for ISOPTIN supplies, using this form, will be granted.

Considering your patient's emergency status, an exception has been made and an initial supply of ISOPTIN is enclosed, consisting of

- ☐ 1 Bottle (150 x 40 mg capsules) Isoptin
- ☑ 2 Bottles (~~150~~ 180 x 80 mg tablets) Isoptin {150-FCFM, 150-SC
- ☑ 2 Bottles (~~360~~ 360 x 120 mg tablets) Isoptin {150-FCFM, 150-SC
- ☐ Ampules (5 mg/2 ml) Isoptin

If this shipment includes a bottle of ISOPTIN tablets, the tearoff portion of the bottle label is to be detached from the bottle, attached to the Follow-up Re-evaluation Form when the bottle is dispensed, and the form is to be returned to Knoll Pharmaceutical Company.

We appreciate your interest in ISOPTIN and will continue to supply it for your patient providing you cooperate with us by filing all the necessary documentation. We hope you understand that this documentation is required by Federal regulations and that by providing this information you will assist us as well as other physicians using the drug.

A seif-addressed postage paid envelope is enclosed for your convenience in returning these forms.

If I can be of any further assistance, please let me know.

Sincerely yours,

Susan S. Martin, R.N., M.A.
Emergency Use Coordinator
(201) 428-8250

In case of emergency, you may also contact:

M.L. Grozier, M.D.
Vice-President, Medical
(201) 867-7362
(201) 766-7917 - Home

* PLEASE COMPLETE SIGN & RETURN

LIST OF PACKAGE CONTENTS

*To be returned to Knoll Pharmaceutical Company

TO WHOM IT MAY CONCERN:

The following material has been supplied to me at my request by Knoll Pharmaceutical Company:

Isoptin(R) - Knoll (verapamil) Investigator's Brochure

* Isoptin(R) - Knoll (verapamil) Protocol V-900- Emergency (compassionate) Use
(Sign and return page 16 - Prescriber's Statement)

* Isoptin(R) - Knoll (verapamil) "Request for Emergen Use Form"

* FD #1573 "Statement of Investigator Form"
(Attach current CV and cardiology board certification numbers/year)

Isoptin(R) - Knoll (verapamil) Case Report Form
(To be completed and returned upon initiation of therapy)

Isoptin(R) - Knoll (verapamil) Follow Up Evaluation Form
(To be completed and returned at intervals not exceeding 2 months and when requesting additional supplies)

Isoptin(R) - Knoll (verapamil) 0 5 mg Ampules

0 40 mg Capsules

150x80.Fam
150x80.SC 300 80 mg Tablets

150x120.Fam
150x120.SC 300 120 mg Tablets

X _____, M.D.
Requesting Physician

TO ALL PHYSICIANS RECEIVING ISOPTIN® (VERAPAMIL HCl) FOR EMERGENCY USE

RE: Concomitant Use of Isoptin and Other Cardioactive Drugs

Until complete data on interactions between Isoptin and other cardioactive drugs are obtained, we consider it to be in the patient's best interest to proceed with utmost caution if Isoptin must be administered concomitantly with other cardioactive drugs (especially antiarrhythmic agents or digitalis). All necessary consideration must be given to the absorption, mechanisms of action, metabolism, elimination kinetics and plasma levels of drugs being considered for concomitant administration.

Digitalis

1. No data presently available indicate that the use of Isoptin in digitalized patients should be contraindicated.

2. Isoptin and digitalis may act synergistically on the AV node and may produce pathologic delay in AV conduction in patients receiving high doses of Isoptin in the presence of excessive digitalization.

3. Preliminary data suggest the possibility that Isoptin may increase blood levels of digitalis if given concomitantly. Until further data are available, patients receiving Isoptin concomitantly with digitalis must be subject to scrutiny for symptoms or signs of digitalis toxicity and should have their digitalis blood levels measured at frequent intervals.

Beta-Adrenergic Blocking Agents

Please be informed that until further data are available, the concomitant use of Isoptin and beta-adrenergic blocking agents such as propranolol is contraindicated.

We hereby inform you that at the present time, it is considered:

a. Contraindicated to administer Isoptin until at least 48 hours have elapsed since the last dose of Inderal or other beta-adrenergic blocking agents.

b. Contraindicated to administer Inderal or other beta-adrenergic blocking agents until at least 48 hours have elapsed since the last dose of Isoptin.

Disopyramide (Norpace® Searle)

Until data are available to prove that deleterious interactions between Isoptin and Norpace do not occur, concomitant administration of these drugs must be avoided. Please be informed that two instances of death in patients who received Isoptin and disopyramide have been reported. Since we do not know if a causal relationship exists, we hereby inform you that at the present time, it is considered:

a. Contraindicated to administer Isoptin until at least 48 hours have elapsed since the last dose of Norpace.

b. Contraindicated to administer Norpace until at least 48 hours have elapsed since the last dose of Isoptin.

Quinidine

An instance of electromechanical uncoupling has been recently reported in a patient with asymmetric septal hypertrophy who was receiving Isoptin and quinidine by mouth. A severe adverse reaction characterized by hypotension, pulmonary edema and hemolysis was described. Although the cause and effect relationship of this adverse reaction is not yet clear, we want to inform you of this incident.

Suggestions for Altering Your Patients' Drug Regimen

If the patient is on therapy with one or more cardioactive drugs, and addition of Isoptin to the regimen is indicated, the dosage of Isoptin should be carefully titrated upward as the dosage of the other drug(s) is decreased or maintained. Similarly, if the patient is on therapy with Isoptin, but the addition of other cardioactive drugs is indicated, the dosage of Isoptin should be lowered. Clinical and electrocardiographic evaluation must be performed as often as the clinical condition requires to detect early signs of deleterious drug interactions.

Finally, we wish to reemphasize the need to exercise utmost caution whenever cardioactive drugs must be used concomitantly with Isoptin. Studies to evaluate drug interactions are in progress, and we will inform you of the results as they become available.

Laboratory testing of your patients (including hematology, blood chemistries, and urinalysis) is of great importance to us in establishing the safety of Isoptin and to you in the close monitoring of the effects of an Investigational Drug as dictated by F.D.A. requirements. Therefore, in order to assure a continued supply of Isoptin for your patients, laboratory data must be attached to all Patient Evaluation Reports at two month intervals. Your request for additional Isoptin supplies will be shipped only upon receipt at Knoll Pharmaceutical Company of the following:

1. Patient Evaluation Report - completed in full and signed.

2. Current laboratory data including:

   a. Hematology (CBC)

   b. Blood chemistries

   c. Digitoxin/Digoxin blood level if patient is receiving either medication and Isoptin concomitantly.

   d. Urinalysis.

Thank you for your cooperation.

Susan Martin, R.N., M.A.
Emergency Use Coordinator
Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, New Jersey 07981
(201) 887-8300, Ext. 192

Juan R. Guerrero, M.D.
Medical Director
Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, New Jersey 07981
(201) 887-8300, Ext. 130

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD • WHIPPANY, NEW JERSEY 07981

August 6, 1980

Dear Doctor:

Recently we have had two separately-reported cases of possible verapamil-warfarin sodium (Coumadin®) interaction in chronic atrial fibrillation patients. Both patients were petite, middle-aged to elderly women (average body weight, 105 lbs.) stabilized on warfarin. After several days of receiving verapamil 80 mg t.i.d., one patient developed a markedly elevated prothrombin time, the other presented with multiple ecchymoses. Both experienced 1+ to 2+ ankle edema. Symptomatic treatment (decreasing anticoagulant and adding diuretics) along with a decrease or discontinuation of verapamil dosage has resulted in reversal of signs and symptoms (i.e., prothrombin time returned to normal).

Please be reminded that inasmuch as both verapamil and warfarin are highly protein-bound (each $\geq$90%) the potential exists for warfarin displacement from plasma albumin resulting in prolongation of prothrombin time. This temporary increase in anticoagulant effect may result in serious hemorrhagic reaction if overlooked.

We therefore urge that caution, patient cooperation and frequent monitoring of blood coagulation studies be exercised in these patients until more is known about verapamil-warfarin interaction.

Sincerely,

Juan R. Guerrero, M.D.
Medical Director

JRG:wpc

TEL.: (201) 887-8300 — TELEX: 136466

✕ COMPLETE, SIGN & RETURN PAGE 16 ONLY (PRESCRIBER'S STATEMENT)

ISOPTIN
(verapamil HCl)

Clinical Protocol No. V-900

PROTOCOL FOR EMERGENCY (COMPASSIONATE) USE OF ISOPTIN WHENEVER A PATIENT HAS NOT RESPONDED TO, OR CANNOT TOLERATE CONVENTIONAL THERAPEUTIC AGENTS

Medical Department
KNOLL PHARMACEUTICAL COMPANY
30 North Jefferson Road
Whippany, New Jersey 07981

November 15, 1979

ISOPTIN (verapamil HCl)
Protocol V-900

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KNOLL PHARMACEUTICAL COMPANY

PROTOCOL FOR EMERGENCY (COMPASSIONATE) USE OF ISOPTIN WHENEVER A PATIENT HAS NOT RESPONDED TO, OR CANNOT TOLERATE CONVENTIONAL THERAPEUTIC AGENTS

I. INTRODUCTION

Verapamil hydrochloride (Isoptin(R)), first marketed in Germany in 1962, has been studied and used widely in clinical practice in Europe and other parts of the world. Verapamil HCl is an organic calcium antagonist reported to have anti-arrhythmic, antianginal and antihypertensive properties in man. Verapamil HCl exerts its pharmacologic effects by blocking the slow channel inward calcium current in the myocardial cell membrane and in smooth muscle cells of the coronary and systemic arteries.

The antianginal effects of verapamil HCl seem to result from the decreasing of resistance in the systemic and coronary vasculature as well as from intracellular oxygen-sparing effects. The net pharmacologic effect seems to be a decrease in myocardial oxygen consumption with concomitant increase in coronary perfusion.

The antiarrhythmic effects of verapamil HCl seem to be due to slowing of conduction across the AV node and prolongation of the AV refractory period. Verapamil HCl does not modify intraatrial, His-Purkinje or intraventricular conduction. Prolongation of the corrected sinus recovery time has been reported after administration of verapamil HCl; therefore, use of verapamil HCl is contraindicated whenever sick sinus syndrome is suspected.

Despite reports attributing negative inotropic effects to verapamil HCl in studies done in animal models and isolated heart preparations, evidence is accumulating to indicate that this is not the case when therapeutic doses are given to man. A recent study done by Ferlinz et al. (1) indicates that intravenous verapamil HCl increases cardiac output, ejection fraction and velocity of circumferential fiber shortening with concomitant reduction of peripheral vascular resistance and no change in the heart rate.

1. Ferlinz J, Easthope J, Aronow W: Effects of Verapamil on Myocardial Performance in Coronary Disease. Circulation 59:313-319, 1979.

Pharmacokinetic studies in man indicate that absorption of orally administered verapamil HCl is almost complete. First-pass metabolism is approximately 70%. A preliminary estimate indicates a 10.5% bioavailability of verapamil HCl when given orally. Preclinical studies indicate that verapamil HCl is metabolized in the liver and excreted (as conjugated metabolites) by the kidneys. Preliminary studies indicate that the half-life of the alpha phase (rapid decline) after single administration of an intravenous bolus is 18 to 31 minutes; the beta phase is 213 to 442 minutes. After oral administration, half-lives of the beta phase ranged from 161 to 201 minutes.

Results of a study done to evaluate the hemodynamic effects of verapamil HCl and practolol suggest that concomitant administration of beta-adrenergic blocking agents and verapamil HCl may produce negative effects on myocardial contractility and should, hence, be avoided. Until complete data on interactions between Isoptin and other cardioactive drugs are obtained, we consider that it is in the patient's best interest to proceed with caution whenever Isoptin must be administered concomitantly with other cardioactive drugs. All necessary consideration must be given to the absorption, mechanisms of action, metabolism, elimination kinetics and plasma levels of drugs considered for concomitant administration. Use of Isoptin whenever digitalis toxicity is diagnosed or suspected, is contraindicated. Use of Isoptin concomitantly with beta-adrenergic blocking agents or with disopyramide (Norpace-Searle) is also contraindicated.

The prescriber and co-prescribers are urged to become thoroughly familiar with the "Isoptin Investigator's Brochure" before initiating therapy with Isoptin (verapamil HCl).

A total of 262 individual studies done overseas were reviewed (see "Isoptin Investigator's Brochure") in which 11,202 patients received treatment with either oral, intravenous or a combination of both formulations of Isoptin for treatment of coronary insufficiency and cardiac arrhythmias. Adequate data for evaluation of adverse effects were available for 8,344 patients. Adverse effects were reported in 739 patients (9%) affecting the following systems: cardiovascular in 302 patients (3.6%); central nervous in 183 patients (2.2%)--mainly headache and dizziness; gastrointestinal in 184 (2.2%)--mainly constipation and nausea; respiratory in 13 (0.2%); and miscellaneous adverse effects in 64 (0.8%).

Intravenous administration of Isoptin may be followed by a mild transient drop in arterial blood pressure which usually occurs shortly after injection and is often asymptomatic. Although the data as reported did not allow complete evaluation of all patients reported in all the studies, 57 patients (0.7%) were identified for whom Isoptin was discontinued because of adverse effects.

Clinical trials to further evaluate the safety and efficacy of Isoptin as treatment for supraventricular tachyarrhythmias and angina pectoris are being implemented in the USA by Knoll Pharmaceutical Company.

II. OBJECTIVES

The objective of this protocol is to provide guidelines for the compassionate use of Isoptin (verapamil HCl) when all the following conditions are fulfilled:

A. Currently available cardioactive drugs have proven ineffective or are not well tolerated by the patient,

B. It is considered by the prescriber, a board-certified cardiologist, to be in the patient's best interest to receive therapy with Isoptin,

C. The prescriber, after assessing the available information, considers that Isoptin may provide greater relief than conventional therapy and/or enhance quality of life.

III. PATIENT SELECTION

A. Criteria for Inclusion

1. Diagnosis

a. Supraventricular tachycardia unresponsive to conventional antiarrhythmic agents.

b. Angina pectoris unresponsive to conventional therapeutic agents including:

i. Angina at rest, e.g., unstable (accelerated) angina, variant (Prinzmetal's) angina, and post-prandial angina.

ii. Angina of effort.

iii. Angina in patients who are not considered candidates for, or who have refused coronary bypass surgery.

iv. Angina in patients who are unable to tolerate therapy with conventional drugs.

c. Other serious life-threatening conditions (e.g., idiopathic hypertrophic sub-aortic stenosis) amenable to therapy with calcium influx inhibitors and for which other conventional therapeutic agents are non-extant, ineffective, intolerated or contraindicated.

2. Patients will be between 21 and 70 years of age.

The benefit-risk ratio for the administration of Isoptin to children and geriatric patients should be carefully assessed since pharmacokinetic data for these groups is not presently available.

3. Women (who are neither pregnant nor lactating) and men may be treated with Isoptin. Women of childbearing potential may be considered eligible for Isoptin therapy only if they are following a medically recognized contraceptive program. A pregnancy test must be negative.

4. Patients must give written informed consent. Obtaining proper informed consent from the patient is the responsibility of the board-certified cardiologist who will be prescribing and administering Isoptin. A copy of this signed informed consent must be kept in the cardiologist's file for this patient.

B. Criteria For Exclusion

1. Congestive heart failure as characterized by any combination of the following: Cardiomegaly, hepatomegaly, alveolar rales, S_3 gallop, venous hypertension, pulmonary wedge pressure greater than 16 mmHg, cardiac index less than 2.0 liters/min/m^2.

2. Severe uncontrolled hypertension (diastolic blood pressure greater than 115 mmHg).

3. Systolic blood pressure less than 90 mmHg.

4. Left bundle branch block (unless patient has an adequately functioning implanted ventricular pacemaker).

5. Severe bradycardia (less than 50 beats/min) or fixed AV block 1st degree or greater unless the patient has an adequately functioning implanted ventricular pacemaker.

6. Sick sinus syndrome unless the patient has an adequately functioning implanted ventricular pacemaker.

7. Development of myocardial necrosis as evidenced by a rise in cardiac enzymes (e.g., CPK-MB fraction) and/or electrocardiographic changes (e.g., development of new Q waves) within 6 weeks prior to initiation of Isoptin.

8. Valvular or congenital cardiac lesions which cause severe hemodynamic impairment.

9. Atrial flutter or atrial fibrillation associated with pre-excitation syndromes (e.g., Wolff-Parkinson-White syndrome).

10. Therapy with beta-adrenergic blocking agents or disopyramide (Norpace, Searle) 48 hours or less before administration of Isoptin.

11. Need for concomitant therapy with antiarrhythmic agents other than digitalis, lidocaine or procainamide.

12. Use of an investigational drug (other than Isoptin) in the 8 days prior to administration of Isoptin.

13. Evidence or suspicion of digitalis toxicity (e.g., digitalis-induced arrhythmias).

14. Clinically significant renal failure (e.g., serum creatinine over 2 mg%).

15. Clinically significant hepatic failure (e.g., serum bilirubin greater than 2.0 mg% and/or SGOT or SGPT levels greater than three times the high normal limit for the method used).

16. Clinically significant electrolyte imbalance (e.g., serum potassium lower than 3.0 mEq/l or greater than 5.5 mEq/l).

17. Terminal illness.

18. Unwillingness or inability to cooperate or to give written informed consent.

IV. DRUG SUPPLIES AND LABELING

Isoptin (verapamil HCl) is available as 5 mg in 2 ml ampules for intravenous use and in tablets of 80 mg and 120 mg for oral administration. It is also available as 40 mg capsules to be used whenever extra caution during dose titration may be advisable.

Knoll Pharmaceutical Company will initially supply no more than four Isoptin ampules or no more than 150 (80 mg) tablets, unless the physician can justify the need for more supplies.

Accurate accounting of investigational drugs is mandatory under FDA regulations. Federal guidelines require that an inventory of investigational drug supplies should be kept by the prescribing physician.

Under no circumstances is the recipient of clinical supplies allowed to release Isoptin for use by another physician not named on FDA 1573 "Statement of Investigator Form" or to administer Isoptin to a patient for whom proper documentation has not been previously filed with Knoll Pharmaceutical Company.

Only written requests for additional Isoptin will be acknowledged.

The bottles containing Isoptin tablets and the boxes containing Isoptin ampules have duplicate tear-off labels which must be detached when the bottle or ampules are dispensed to the patient and attached to the Follow-Up Evaluation Report on which additional clinical supplies are requested.

Isoptin will be supplied for continued treatment only when Knoll Pharmaceutical Company has received all requested documentation listed below:

- FDA 1573 Statement of Investigator Form

- Request for Emergency Use Form

- Case Report Form

- Follow-Up Evaluation Form along with evidence that the patient has had a successful clinical response in the absence of clinically significant adverse reactions.

Initial and follow-up supplies of Isoptin must be requested for each individual patient. It must be kept in mind that at least 2 weeks are needed for documentation handling, drug shipment and delivery.

Sudden discontinuation of Isoptin therapy is to be avoided. To prevent this risk, upon receipt (at Knoll Pharmaceutical Company) of the first Follow-Up Evaluation Report, an adequate reserve supply (one bottle with 150 Isoptin tablets of the strength requested) will be sent to the prescriber. This reserve supply must be kept, at all times, at the cardiologist's office. This supply is to be used only if there is a delay in drug shipment, delivery or loss of medication by the patient. The reserve supply is labeled RESERVE in red ink. If it must be dispensed, detach the duplicate tear-off label and attach it to the "Follow-Up Evaluation Form" with an explanation of the circumstances which warranted use of the reserve supply. Only upon receipt at Knoll Pharmaceutical Company of this duplicate RESERVE label and an explanation of circumstances warranting its use, will a replacement reserve supply be sent for the patient.

If Isoptin therapy is discontinued, all unused supplies must be returned immediately to Knoll Pharmaceutical Company as required by federal regulations for investigational new drugs. Isoptin supplies allocated for a patient may not be retained and/or used for any patient other than the one for whom originally assigned.

V. DRUG DOSAGE AND REGIMEN OF ADMINISTRATION

Available clinical experience with Isoptin (verapamil HCl) suggests that the following doses are efficacious and well tolerated:

A. Intravenous Formulation

- Single Dose: 0.075 mg/kg to 0.150 mg/kg given to a maximum total single dose of 5 to 10 mg per injection.

Isoptin can be given as a bolus injection in a minimun of 1 to 2 minutes except in elderly patients and/or patients in whom cerebral vascular disease exists or is suspected. In such patients, bolus injections should last 3 to 4 minutes because of the risk of orthostatic hypotension.

- Repeat Dose: If the lower dose (0.075 mg/kg to a maximun of 5 mg) is used and a satisfactory response did not occur, the higher dose may be administered after 30 minutes have elapsed. If the higher dose is used initially and a satisfactory response is not obtained, a second similar dose can be administered 45 minutes after the first dose, provided no adverse effects occur with the first dose and the patient's EKG is closely monitored.

B. Oral Formulation

The following are guidelines for ascending dose titration of the oral formulation providing that symptoms are not well controlled with a given dose and that there are no clinically significant adverse reactions. According to overseas experience, the safe and efficacious total daily dosage of oral Isoptin ranges from 240 mg to 480 mg per day. It is recommended to initiate therapy with 80 mg three times a day and increase the daily dose according to the patient's clinical response from the safety and efficacy points of view.

1. 80 mg q8h

2. (80 mg q6h for those patients whose response is adequate but whose duration response is not satisfactory)

3. 120 mg q8h

4. 120 mg q6h. A dose of 120 mg qid or 480 mg per 24 hrs should not be exceeded.

40 mg capsules

Should be used whenever extra caution in dose titration is advisable (e.g., with recent withdrawal from chronic therapy with beta-adrenergic blocking agents or in the presence of left ventricular dysfunction) until complete data on drug interactions and hemodynamic effects of calcium antagonists on patients with diminished left ventricular function have been obtained.

VI. PROCEDURES

All data obtained when implementing the procedures indicated below must be entered in the patient Case Report Form (CRF) provided by Knoll Pharmaceutical Company. The prescriber is to retain a copy of the CRF for his permanent files and send the original to Knoll Pharmaceutical Company (Att. Ms. Susan Martin, R.N., M.A.).

A. Clinical Evaluations

Patients considered as candidates for Isoptin therapy must give a complete medical history and undergo a complete physical examination prior to receiving Isoptin. Interim clinical evaluations, including assessment of new symptomatology, and interim physical examinations will be done:

- at least once a day while hospitalized

- at least once every two months, or more often if deemed necessary, for as long as Isoptin is given on an outpatient basis.

Interim clinical evaluations must include (but not be limited to) a complete examination of the cardiorespiratory systems, a search for changes in relation to the baseline physical examination, and a thorough search for adverse reactions. Heart rate, respiratory rate and blood pressure (a mercury column sphygmomanometer, a proper size cuff, the right arm and phase V of the Korotkoff sound will be used to determine blood pressure) will also be measured at each visit.

Until further data are obtained, gradual withdrawal (25% decrements in total daily dose) from Isoptin therapy is recommended. A follow-up clinical evaluation must be done and the data filed with Knoll Pharmaceutical Company no longer than 1 week after discontinuation of therapy with Isoptin.

B. Electrocardiographic Monitoring and Recording

A 12-lead electrocardiogram should be taken before initiation of Isoptin therapy. Follow-up 12-lead electrocardiograms and/or Holter recordings should be done as often as the prescriber deems in the patient's best interest and as often as needed to accurately assess the patient's response to Isoptin.

The P-Q interval may increase in relation to the effect of Isoptin on conduction across the AV node. Preliminary data indicate that peak electrophysiologic effects occur at approximately 1 hour after administration of the oral formulation. To monitor the electrophysiologic effects of Isoptin, measuring the P-Q interval at this time may be useful.

C. Chest X-Rays

A teleroentgenogram of the chest should be done prior to initiation and immediately after discontinuation of Isoptin therapy. Follow-up teleroentgenograms will be done as the prescriber deems necessary.

D. Ophthalmologic Examinations

As suggested by the Food and Drug Administration for all systemically absorbed investigational drugs, proof of opthalmological safety should be obtained. To achieve this purpose, the following is requested:

> Prior to the patient reaching 30 days of Isoptin therapy, a complete ophthalmologic examination with photographic documentation of any lens opacities should be obtained whenever chronic therapy is anticipated.

Periodic evaluations should be performed at least once every 6 months while on Isoptin therapy and 4 to 6 months after its discontinuation.

E. Clinical Laboratory Evaluations

Samples of blood and urine for the following tests should be obtained prior to initiation of Isoptin therapy and at least once every 2 months or more often if deemed necessary.

1. Complete routine urinalysis (including microscopic examination of the sediment).

2. Hemoglobin, hematocrit, WBC count, differential and platelet count.

3. Blood glucose, blood urea nitrogen (BUN), uric acid, serum creatinine, cholesterol, serum glutamic oxaloacetic transaminase (SGOT), calcium, total bilirubin, phosphorus, alkaline phosphatase, total protein, albumin, lactic acid dehydrogenase (LDH), creatine phosphokinase-MB fraction (quantitative CPK-MB), sodium (Na^+), and potassium (K^+).

4. Digitalis blood level (if digitalis is being administered concomitantly).

Your cooperation in obtaining laboratory data and filing the results with Knoll Pharmaceutical Company will enable us to continue supplying Isoptin for your patient.

VII. CONCOMITANT MEDICATION

Until data on drug interactions are available the use of beta-adrenergic blocking agents and/or disopyramide phosphate (Norpace, Searle) is contraindicated 48 hours before, during, and 48 hours after administration of Isoptin. Also, until complete data on interactions with other cardioactive drugs are obtained, we consider it to be in the patient's best interest to proceed with caution if Isoptin must be administered concomitantly with any other cardioactive drugs.

Use of drugs not included under "Criteria for Exclusion" should be documented in the patient's case report form.

Isoptin and cardiac glycosides may act synergistically on the AV node. Excessive digitalization may produce pathologic delay in AV conduction when high doses of Isoptin are given. Although such electrophysiological effects are possible and caution should be exercised when using the combination, there is no data to suggest that the use of Isoptin in digitalized patients should be contraindicated.

Therefore, this protocol will allow the use of Isoptin in patients who are fully digitalized as long as patients are carefully followed and there is no suspicion or symptoms of digitalis toxicity or decompensated cardiac function. Minor alterations of digitalis dosage are permissible if the patient is under close monitoring by a board-certified cardiologist.

VIII. CRITERIA FOR DISCONTINUING THERAPY

The following events are considered sufficient reason to discontinue treatment with Isoptin:

A. Whenever the patient decides that it is in his/her best interest.

B. Whenever the prescriber deems it necessary or in the patient's best interest.

C. Whenever clinically significant and/or severe adverse effects occur.

D. Whenever pregnancy is diagnosed.

E. Whenever myocardial infarction occurs.

If a patient is withdrawn from Isoptin, the reason for discontinuation and all pertinent documentation must be reported promptly and in full to Knoll Pharmaceutical Company. Any remaining unused supplies of Isoptin must be promptly returned to Knoll. Unused drug supplies may not be retained by the prescriber for use by another patient.

IX. PROCEDURE FOR DISCONTINUATION OF ISOPTIN THERAPY

A complete physical examination, a 24-hour magnetic tape recording if indicated, a 12-lead electrocardiogram and rhythm strip (1-min recording of Lead II), a complete set of laboratory studies and a teleroentgenogram of the chest should be obtained 72 hours after a patient is withdrawn from Isoptin therapy. The dosage of Isoptin should be gradually decreased by daily decrements of approximately 25% to prevent the possibility of a "withdrawal" phenomenon (however, such occurrences have not been documented with Isoptin). The reason for discontinuation of Isoptin therapy must be clearly stated in the case report form.

X. ADVERSE REACTIONS

All adverse reactions should be handled as the clinical situation indicates. Clinically significant hypotensive reactions should be treated with vasopressor agents.

High degree AV block and asystole may be handled by the usual measures including appropriate drug therapy, cardiac pacing or cardiopulmonary resuscitation. (See "Isoptin Investigator's Brochure" for more information.) Instances of deliberate overdose (up to 2 gms taken orally) with Isoptin

have been reported. Hypotension, sinus node depression, repolarization changes and A-V Block (including A-V dissociation) have been described, and in at least one reported case calcium gluconate was used effectively.[2]

All clinically significant or serious adverse reactions will be reported immediately by telephone and in writing to:

Susan B. Martin, R.N. M.A.
Emergency Use Coordinator
KNOLL PHARMACEUTICAL COMPANY
30 North Jefferson Road
Whippany, NJ 07981

Telephone: 201/887-8300
Ext. 192

or

Juan R. Guerrero, M.D.
Medical Director
KNOLL PHARMACEUTICAL COMPANY
30 North Jefferson Road
Whippany, NJ 07981

Telephone: 201/887-8300
201/359-7243

or

Edward B. Kirsten, Ph.D.
Director of Clinical Pharmacology
KNOLL PHARMACEUTICAL COMPANY
30 North Jefferson Road
Whippany, NJ 07981
Telephone: 201/887-8300
201/667-0783

Upon receipt of notification of a clinically significant reaction, an FD 1639 form will be forwarded to the prescriber. An FD 1639 Form must be completed for all clinically significant, severe and/or unusual adverse reactions. The FD 1639 Form must be returned to the Knoll Pharmaceutical Company within 5 days of its receipt by the prescriber or within 10 days of the occurrence of the adverse reaction.

2Perkins, C. Serious verapamil poisoning: treatment with intravenous calcium gluconate. British Medical Journal 2:1127, Oct. 1978.

XI. INFORMED CONSENT

Before a patient is treated with Isoptin, the nature, purposes and known risks of therapy with this investigational drug as well as possible adverse effects of Isoptin must be explained to the patient in the presence of a witness. The patients must sign an informed consent form indicating that he/she has given his/her consent to receive Isoptin. Each signature is to be witnessed. The signed informed consent form must be kept on file by the prescriber.

XII. INSTITUTIONAL REVIEW

If applicable, the prescriber will submit this protocol and the informed consent form to be used to his/her Institutional Review Committee.

XIII. RECORDING AND PROCESSING DATA

All required data will be recorded on case report forms supplied by Knoll Pharmaceutical Company. All completed case report forms must be signed and dated by the prescriber. A reasonable explanation must be given under "Comments" for all required information missing from a case report form.

XIV. PRESCRIBER'S RECORDS REQUIREMENTS

Federal regulations require that copies of case report forms and other pertinent documentation (e.g., original ECG tracings, laboratory reports, hospital or office patient records, etc.) be retained by the prescriber for a period of 2 years following either the approval of the New Drug Application or withdrawal of the Investigational New Drug application. The Knoll Pharmaceutical Company will advise the prescriber when the 2-year period begins.

Attention of the prescriber is drawn to the fact that he/she may be subjected to a field audit by FDA inspectors in order to validate warranted emergency (compassionate) use of Isoptin. With this in mind, careful attention should be paid to seeing that complete patient's records including data on Isoptin and all othe drugs as well as originals of electrocardiograms, laboratory tests, x-rays, etc. are filed in the patient's hospital or office record.

XV. DEVIATION FROM PROTOCOL

No deviations from this protocol will be permitted without the approval of the Medical Monitor of the Knoll Pharmaceutical Company.

XVI. UNUSED STUDY MEDICATION

By signing this protocol, the prescriber agrees to follow it and to be accountable for any unused drug supplies. To comply with federal regulations, the prescriber must promptly return all remaining drug and pertinent documentation to the Knoll Pharmaceutical Company at the termination of Emergency Use of Isoptin. At termination of therapy, a "Disposition of Investigational New Drug" form must be completed and returned to Knoll Pharmaceutical Company.

XVII. DISCLOSURE OF DATA

Please keep in mind that all data transmitted to you is highly confidential in nature and must be kept as such. The author will notify Knoll Pharmaceutical Company, prior to any publication or oral presentation of the data resulting from emergency use of Isoptin. A copy of the presentation or paper must be submitted to the sponsor prior to presentation or publication. All information supplied to Knoll Pharmaceutical Company will remain confidential and will be treated as such when submitted to the Food and Drug Administration.

Please read, sign and detach this form. Send the original to Knoll Pharmaceutical Company. Retain a copy for your files.

XVIII. PRESCRIBER'S STATEMENT

A. I have received and reviewed the Isoptin Investigator's Brochure.

B. I am attaching to this document the following required forms:

|✓| yes |_| no - FDA #1573 Statement of Investigator Form

|✓| yes |_| no - Current curriculum vita and cardiology board certification number and/or year attached.

|✓| yes |_| no - Request for Emergency Use Form XZ

|✓| yes |_| no - List of package contents received

C. I have carefully read Protocol V-900 for Emergency (Compassionate) Use of Isoptin. I agree to follow it and to provide Knoll Pharmaceutical with all required documentation.

X _____
Date

X _____, M.D.
Cardiologist responsible for prescribing and administering Isoptin

ATTACH CURRENT CV & CARDIOLOGY BOARD CERTIFICATION (BD./YR.) IF A CARDIOLOGIST AS LISTED ON PAGE 2. SIGN & RETURN TO A.P.C.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION 5600 FISHERS LANE ROCKVILLE, MARYLAND 20857	**STATEMENT OF INVESTIGATOR**	*Form Approved* *OMB No. 57-R0029* *Use of this form is prohibited after December 31, 1980*

NOTE: No drug may be shipped or study initiated unless a completed statement has been received (21 *CFR 312.1(a) (12),*).

TO: SUPPLIER OF DRUG *(Name and address, include Zip Code)*	NAME OF INVESTIGATOR *(Print or Type)*
Knoll Pharmaceutical Company 30 North Jefferson Rd. Whippany, N.J. 07981	Jerome Ryan, M. D.
	DATE March 18, 1981
	NAME OF DRUG Isoptin

Dear Sir:

The undersigned, _____ submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 312.1 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical investigations with a new drug limited by Federal *(or United States)* law to investigational use.

1. STATEMENT OF EDUCATION AND EXPERIENCE

a. COLLEGES, UNIVERSITIES, AND MEDICAL OR OTHER PROFESSIONAL SCHOOLS ATTENDED, WITH DATES OF ATTENDANCE, DEGREES, AND DATES DEGREES WERE AWARDED

b. POSTGRADUATE MEDICAL OR OTHER PROFESSIONAL TRAINING *(Indicate dates, names of institutions, and nature of training)*

c. TEACHING OR RESEARCH EXPERIENCE *(Indicate dates, institutions, and brief description of experience)*

d. EXPERIENCE IN MEDICAL PRACTICE OR OTHER PROFESSIONAL EXPERIENCE *(Indicate dates, institutional affiliations, nature of practice, or other professional experience)*

e. REPRESENTATIVE LIST OF PERTINENT MEDICAL OR OTHER SCIENTIFIC PUBLICATIONS *(Indicate titles of articles, name of publications and volume, page number, and date)*

FORM FDA 1573 (4/79) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

4. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS, GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE, GOVERN HIS RECEIPTS AND USE OF THIS INVESTIGATIONAL DRUG:

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantities, and use by subjects, and if the investigation is terminated, suspended, discontinued, or completed, to return to the sponsor any unused supply of the drug. If the investigational drug is subject to the Comprehensive Drug Abuse Prevention and Control Act of 1970, adequate precautions must be taken including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

c. The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.

d. The investigator is required to furnish his reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained by various investigators. The sponsor is required to present progress reports to the Food and Drug Administration at appropriate intervals not exceeding 1 year. Any adverse effect that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming, it shall be reported immediately. An adequate report of the investigation should be furnished to the sponsor shortly after completion of the investigation.

e. The investigator shall maintain the records of disposition of the drug and the case histories described above for a period of 2 years following the date a new-drug application is approved for the drug; or if the application is not approved, until 2 years after the investigation is discontinued. Upon the request of a scientifically trained and properly authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The subjects' names need not be divulged unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied, or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered ~~only to subjects under his personal~~ supervision or ~~under the supervision of the following~~ investigators responsible to him:

C. T. Ray M.D
W. LaCourse M.D.
A. Jain M.D.

and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any subjects including subjects used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

h. The investigator is required to assure the sponsor that for investigations involving institutionalized subjects, the studies will not be initiated until the institutional review committee has reviewed and approved the study. (The organization and procedure requirements for such a committee should be explained to the investigator by the sponsor as set forth in Form FD 1571, division 10, unit c.

Very truly yours,

* Jerome R. Ryan M.D
(Name of Investigator)

(Address)

(This form should be supplemented or amended from time to time if new subjects are added or if significant changes are made in the plan of investigation.)

REQUEST FOR EMERGENCY USE OF ISOPTIN® (verapamil HCl)

RETURN TO:
MEDICAL DEPARTMENT
KNOLL PHARMACEUTICAL COMPANY
30 JEFFERSON ROAD
WHIPPANY, NJ 07981

DATE MAILED: 3/18/81

PLEASE COMPLETE, SIGN AND RETURN

PHYSICIAN INFORMATION

NAME, ADDRESS, PHONE NUMBER AND ACADEMIC AFFILIATION OF PHYSICIAN REQUESTING ISOPTIN

Jerome Byrd MD.
Professor of Medicine
1430 Tulane Ave
New Orleans, Louisiana 70112

TEL 504-581-1575

BOARD CERTIFIED CARDIOLOGIST?

☐ No ☐ Yes (If no, please indicate a Board Certified Cardiologist who will supervise the use of Isoptin.)

HOW DID THE PHYSICIAN LEARN ABOUT ISOPTIN: _____

CLINICAL INFORMATION

PATIENT INITIALS FGM

SEX M

AGE 57

DATE OF BIRTH 9 (MO) 10 (DA) 23 (YR)

☑ OUTPATIENT
☐ INPATIENT
HOSPITAL SERVICE _____
☐ CORONARY CARE UNIT
☐ INTERMEDIATE CARE UNIT
OTHER _____

NAME OF INSTITUTION WHERE PATIENT IS BEING TREATED: _____

PRIMARY DIAGNOSIS: Recurrent Atrial Fibrillation

CONCOMITANT DIAGNOSES? ☐ No ☐ Yes (IF YES, Specify) _____

REASONS WHY ISOPTIN SHOULD BE ADMINISTERED TO THIS PATIENT:
☐ Failure to respond to conventional therapy
☒ Refractory to conventional therapy
☐ Intolerant to conventional therapy
☐ Other (Specify) _____

BRIEF HISTORY OF THE DISEASE TO BE TREATED WITH ISOPTIN:
Patient is having episodes of atrial fibrillation approximately every 3 days

ST-T CHANGES ☒ No ☐ Yes SIGNIFICANT HYPOTENSION ☒ No ☐ Yes

ELECTROPHYSIOLOGIC STUDIES ☒ No ☐ Yes DATE: _____ PRE-EXCITATION PATHWAY ☒ No ☐ Yes

DURATION OF DISEASE: 3 years FREQUENCY: q 3 days SEVERITY: Moderate HEART RATE (Ventricular) 120

KNOLL PHARMACEUTICAL COMPANY

* NCR Breakdown
White — MEDICAL DEPT. Green — MDC
Blue — REGULATORY AFFAIRS Canary — PRESCRIBER

V-E-1

CLINICAL INFORMATION (CONTINUED)

HAS PATIENT SHOWN ANY SIGNS OF:

		IF YES, SPECIFY
KIDNEY FAILURE	☑ No ☐ Yes	
LIVER FAILURE	☑ No ☐ Yes	
CARDIAC FAILURE	☑ No ☐ Yes	
ALLERGIES (include drugs)	☑ No ☐ Yes	

DRUGS USED AND PATIENT'S RESPONSE:

DRUG NAME	DAILY DOSE/ ROUTE	RESPONSE TO THERAPY	IS THERAPY TO BE CONTINUED
Digitalis	0.25	None	☑ No ☐ Yes
Quinidine	400 mg	poor	☑ No ☐ Yes
Propranolol	160	poor	☑ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes

SUPPLIES REQUESTED

PHYSICIAN'S ESTIMATE OF AMOUNT OF ISOPTIN NEEDED FOR THIS PATIENT:

Route of Administration: ☑ Oral ☐ IV

Single Dose: ☐ 40 mg ☑ 80 mg ☑ 120 mg ☐ 5 mg - 10 mg

Regimen of Administration: q8-6h

Disopyramide (Norpace) and Beta-Adrenergic Blockers Are CONTRAINDICATED FOR 48 Hours Prior To Isoptin Administration.

NUMBER REQUESTED

ISOPTIN AMPULES (5 mg each) _____ (ampules)

ISOPTIN CAPSULES (40 mg each) _____ capsules (150 minimum)

ISOPTIN TABLETS (80 mg each) 150 tablets (150 minimum)

(120 mg each) 150 tablets (150 minimum)

Documentation Sent ☐

Documentation & Drug Sent ☑

Accurate accounting of Isoptin supplies must be kept. Any unused Isoptin must be returned to Knoll Pharmaceutical Company. All requests for additional supplies of Isoptin must be in writing.

MISCELLANEOUS

An FDA Form # 1573 is attached and must be returned with your Curriculum Vitae. Your signature on this form signifies your willingness to provide Knoll Pharmaceutical Company with appropriate follow-up documentation on this patient.

X _____ Signature of Board Certified Cardiologist

X _____ Date

FOR KNOLL PHARMACEUTICAL COMPANY USE ONLY

INFORMATION TAKEN BY: Michael Grogan MD transcribed by Susan Martin RN MS 3/18/91 Date

APPROVED BY: _____ Date

KNOLL PHARMACEUTICAL COMPANY

NCR Breakdown White — MEDICAL DEPT. Blue — REGULATORY AFFAIRS Green — MDC Canary — PRESCRIBER V-E-2

Jerome Regan MD

* *PLEASE COMPLETE, SIGN AND RETURN AFTER INITIATION OF ISOPTIN THERAPY

ISOPTIN
(verapamil HCl)

EMERGENCY-USE

CASE REPORT FORM

INSTRUCTIONS FOR COMPLETION OF ISOPTIN (verapamil) CASE REPORT FORMS

1. Use only black ballpoint pen. The first 12 pages (Hospital Record) should be forwarded to Knoll Pharmaceutical Company upon discharge from the hospital.
2. An explanation must be given for the omission of any data required. Complete all applicable sections of Isoptin as an outpatient
3. Every completed page in the case report folder must be dated and either signed or initialed by the requesting physician.
4. Obtain blood and urine samples before ISOPTIN administration and periodically thereafter while patient is receiving ISOPTIN. See Lab Tests, pp. 10-11.
5. If long term (i.e., more than 3 months) ISOPTIN therapy is indicated, periodic evaluations including lab data, ECG, vital signs, etc. should be performed at intervals not longer than 2 months.
6. Slit-lamp examinations should be performed on all patients expected to receive ISOPTIN for longer than 30 days.
7. Additional follow-up information is requested at 2-month intervals during ISOPTIN therapy. Several 2-page summaries of the patient's medical status have been enclosed for your assistance in reporting this information to us. At this time, additional supplies of ISOPTIN may be requested by completing the bottom portion of the form.

PATIENT INITIALS FGM (M57)

HOSPITAL RECORD NO. _____

KNOLL PHARMACEUTICAL COMPANY

30 NORTH JEFFERSON ROAD
WHIPPANY, NEW JERSEY 07981

(201) 887-8300 Ext. 192

ATTENTION: SUSAN S. MARTIN, R.N., M.A.

ISOPTIN (verapamil) Emergency-Use

Date _____

Physician's Name _____ (print)

Patient Initials _____

Was necessary written informed consent been obtained from the patient? ☐ No ☐ Yes

If Not, was it in the best interest of the patient? (Give reason) _____

RACE Caucasian ☐ Black ☐ Oriental ☐ Other ☐ (Specify) _____

SEX Male ☐ Female ☐ HEIGHT ☐☐☐ cm WEIGHT ☐☐☐ Kg

DATE OF BIRTH ☐☐ Mo ☐☐ Day ☐☐ Yr AGE ☐☐ Years

PHYSICAL EXAMINATION

SYSTEM	NORMAL	ABNORMAL	SPECIFY
Eye, ear, nose and throat	☐	☐	
Cardiac	☐	☐	
Peripheral Vascular	☐	☐	
Pulmonary	☐	☐	
Musculoskeletal	☐	☐	
Gastrointestinal	☐	☐	
Genitourinary	☐	☐	
Neurological	☐	☐	
Endocrine	☐	☐	
Psychiatric	☐	☐	
Lymphatic	☐	☐	
Dermatologic	☐	☐	
Subcutaneous tissues (edema)	☐	☐	
Other	☐	☐	

Comments _____

EXAMINATION OF OPTIC FUNDI

HYPERTENSIVE RETINOPATHY ☐ No ☐ Yes (If "Yes," specify below)

GRADE I. Narrowing of Arterial Lumen ☐ III. Hemorrhages & Exudates ☐

II. Arteriovenous Nicking ☐ IV. Papilledema ☐

Comments _____

HEART RATE ☐☐☐ /minute RESPIRATION ☐☐ /minute

Blood Pressure (mm Hg) (Right arm, Any of 3 readings)

Supine ☐☐☐ / ☐☐☐

The signature of the investigator on Page 1 of this case report form and his initials on all succeeding pages verifies that he has reviewed the data recorded.

Investigator's Signature _____ Date of Record Review _____

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency-Use

Date _____

Patient Initials _____

PRESENT MEDICAL STATUS

Primary Diagnosis _____

Acute ☐ Recurrent ☐ Chronic ☐

Comments _____

American Heart Association – Cardiac Status Classification

1. Uncompromised ☐ 3. Moderately Compromised ☐
2. Slightly Compromised ☐ 4. Severely Compromised ☐

Are there any concomitant diagnoses?

☐ No ☐ Yes (Specify) _____

Did patient take any antiarrhythmic drugs (including digitalis) during past three months?

☐ No ☐ Yes (If "Yes," describe below)

DRUG NAME AND DAILY DOSE/ROUTE	HAS DRUG BEEN DISCONTINUED (If "Yes," indicate date)	RESPONSE TO THERAPY	ADVERSE EFFECTS
DRUG: _____ DOSE/ROUTE:	☐ No ☐ Yes Mo Day Yr.	☐ Excellent ☐ Good ☐ Fair ☐ Poor	☐ No ☐ Yes ☐ Unknown TYPE _____
DRUG: _____ DOSE/ROUTE:	☐ No ☐ Yes Mo Day Yr.	☐ Excellent ☐ Good ☐ Fair ☐ Poor	☐ No ☐ Yes ☐ Unknown TYPE _____
DRUG: _____ DOSE/ROUTE:	☐ No ☐ Yes Mo Day Yr.	☐ Excellent ☐ Good ☐ Fair ☐ Poor	☐ No ☐ Yes ☐ Unknown TYPE _____

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency-Use

Date _____

Patient Initials _____

PRESENT MEDICAL STATUS

If the following spaces are not needed to continue recording antiarrhythmic medication, please proceed to the instructions at the middle of this page

DRUG NAME AND DAILY DOSE/RDUTE	HAS DRUG BEEN DISCONTINUED (If "Yes," indicate date)	RESPONSE TO THERAPY	ADVERSE EFFECTS
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes Mo Day Yr	☐ Excellent ☐ Good ☐ Fair ☐ Poor	☐ No ☐ Unknown ☐ Yes TYPE _____
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes Mo Day Yr	☐ Excellent ☐ Good ☐ Fair ☐ Poor	☐ No ☐ Unknown ☐ Yes TYPE _____
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes Mo Day Yr	☐ Excellent ☐ Good ☐ Fair ☐ Poor	☐ No ☐ Unknown ☐ Yes TYPE _____

Is patient receiving other medication, including contraceptives, at the present time?

☐ No ☐ Yes (If "Yes," describe below)

DRUG NAME AND DOSE/RDUTE	IS THERAPY TO BE CONTINUED?	INDICATION
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes	
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes	
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes	
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes	
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes	
DRUG _____ DOSE/RDUTE _____	☐ No ☐ Yes	

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency Use

Date _____

Patient Initials _____

VITAL SIGNS AND MEDICATION RECORD

DATE	TIME OF DAY	ISOPTIN (VERAPAMIL) DOSE ADMINISTERED (mg)	RESPIRATION (Per Minute)	HEART RATE (Beats/Min.)	BLOOD PRESSURE (mm Hg) Supine SYST	DIAS
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					

INITIALS _____, M.D.

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency Use

Date _____

Patient Initials _____

VITAL SIGNS AND MEDICATION RECORD

DATE	TIME OF DAY	ISOPTIN (VERAPAMIL) DOSE ADMINISTERED (mg)	RESPIRATION (Per Minute)	HEART RATE (Beats/Min.)	BLOOD PRESSURE (mm Hg) Supine SYST	DIAS
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					

KNOLL PHARMACEUTICAL COMPANY

INITIALS _____, M.D.

ISOPTIN (verapamil) Emergency Use

Date _____

Patient Initials _____

VITAL SIGNS AND MEDICATION RECORD

DATE	TIME OF DAY	ISOPTIN (VERAPAMIL) DOSE ADMINISTERED (mg)	RESPIRATION (Per Minute)	HEART RATE (Beats/Min.)	BLOOD PRESSURE (mm Hg) SYST	BLOOD PRESSURE (mm Hg) DIAS
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					
	A.M. / P.M.					

INITIALS _____, M.D.

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency-Use

Date _____

Patient Initials _____

IN-PATIENT DAILY EVALUATION

Heart Rate ☐☐☐ /minute Respiration ☐☐☐ /minute Blood Pressure (mm Hg) (Right arm, Avg of 3 readings): Supine ☐☐☐/☐☐☐

Any new symptoms? ☐ No ☐ Yes Specify: _____

PHYSICAL EXAMINATION

SYSTEM	NORMAL	ABNORMAL	SPECIFY
Eye, ear, nose and throat	☐	☐	
Cardiac	☐	☐	
Peripheral Vascular	☐	☐	
Pulmonary	☐	☐	
Musculoskeletal	☐	☐	
Gastrointestinal	☐	☐	
Genitourinary	☐	☐	
Neurological	☐	☐	
Endocrine	☐	☐	
Psychiatric	☐	☐	
Lymphatic	☐	☐	
Dermatological	☐	☐	
Subcutaneous tissues (edema)	☐	☐	
Other	☐	☐	

Comments _____

EXAMINATION OF OPTIC FUNDI

HYPERTENSIVE RETINOPATHY. ☐ No ☐ Yes (If "Yes," specify below)

GRADE I. Narrowing of Arterial Lumen ☐ III. Hemorrhages & Exudates ☐

II. Arteriovenous Nicking ☐ IV. Papilledema ☐

Comments _____

American Heart Association Cardiac Status Classification 1. Uncompromised ☐ 2. Slightly Compromised ☐ 3. Moderately Compromised ☐ 4. Severely Compromised ☐

Were there any additions, deletions or other changes in concomitant medications?

☐ No ☐ Yes (If "Yes," complete section below)

DRUG	NEW DOSE / ROUTE	CODE	REASON	DATE(S) OF ADMINISTRATION
		☐ Addition ☐ Deletion ☐ Change		From _____ To
		☐ Addition ☐ Deletion ☐ Change		From _____ To
		☐ Addition ☐ Deletion ☐ Change		From _____ To

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency-Use

Date _____

Patient Initials _____

IN-PATIENT DAILY EVALUATION:

Heart Rate ☐☐☐ /minute Respiration ☐☐☐ /minute Blood Pressure (mm Hg) (Register avg. of 2 readings) Supine ☐☐☐ / ☐☐☐

Any new symptoms? ☐ No ☐ Yes Specify: _____

PHYSICAL EXAMINATION

SYSTEM	NORMAL	ABNORMAL	SPECIFY
Eye, ear, nose and throat	☐	☐	
Cardiac	☐	☐	
Peripheral Vascular	☐	☐	
Pulmonary	☐	☐	
Musculoskeletal	☐	☐	
Gastrointestinal	☐	☐	
Genitourinary	☐	☐	
Neurological	☐	☐	
Endocrine	☐	☐	
Psychiatric	☐	☐	
Lymphatic	☐	☐	
Dermatologic	☐	☐	
Subcutaneous tissues (edema)	☐	☐	
Other	☐	☐	

Comments _____

EXAMINATION OF OPTIC FUNDI

HYPERTENSIVE RETINOPATHY ☐ No ☐ Yes (If "Yes," specify below)

GRADE I. Narrowing of Arterial Lumen ☐ III. Hemorrhages & Exudates ☐

II. Arteriovenous Nicking ☐ IV. Papilledema ☐

Comments _____

American Heart Association Cardiac Status Classification 1. Uncompromised ☐ 2 Slightly Compromised ☐

3 Moderately Compromised ☐ 4 Severely Compromised ☐

Were there any additions, deletions or other changes in concomitant medications?

☐ No ☐ Yes (If "Yes," complete section below)

DRUG	NEW DOSE / ROUTE	CODE	REASON	DATE(S) OF ADMINISTRATION
		☐ Addition ☐ Deletion ☐ Change		From _____ To
		☐ Addition ☐ Deletion ☐ Change		From _____ To
		☐ Addition ☐ Deletion ☐ Change		From _____ To

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency-Use

Date _____

Patient Initials _____

IN-PATIENT DAILY EVALUATION

Blood Pressure (mm Hg) (Right arm. Avg of 3 readings)

Heart Rate ☐☐☐ /minute Respiration ☐☐☐ /minute Supine ☐☐☐ / ☐☐☐

Any new symptoms? ☐ No ☐ Yes Specify: _____

PHYSICAL EXAMINATION

SYSTEM	NORMAL	ABNORMAL	SPECIFY
Eye, ear, nose and throat	☐	☐	
Cardiac	☐	☐	
Peripheral Vascular	☐	☐	
Pulmonary	☐	☐	
Musculoskeletal	☐	☐	
Gastrointestinal	☐	☐	
Genitourinary	☐	☐	
Neurological	☐	☐	
Endocrine	☐	☐	
Psychiatric	☐	☐	
Lymphatic	☐	☐	
Dermatologic	☐	☐	
Subcutaneous tissues (edema)	☐	☐	
Other	☐	☐	

Comments: _____

EXAMINATION OF OPTIC FUNDI

HYPERTENSIVE RETINOPATHY: ☐ No ☐ Yes (If "Yes," specify below)

GRADE I. Narrowing of Arterial Lumen ☐ III. Hemorrhages & Exudates ☐

II. Arteriovenous Nicking ☐ IV. Papilloedema ☐

Comments: _____

American Heart Association Cardiac Status Classification 1. Uncompromised ☐ 2 Slightly Compromised ☐

3 Moderately Compromised ☐ 4 Severely Compromised ☐

Were there any additions, deletions or other changes in concomitant medications?

☐ No ☐ Yes (If "Yes," complete section below)

DRUG	NEW DOSE / ROUTE	CODE	REASON	DATES OF ADMINISTRATION
		☐ Addition ☐ Deletion ☐ Change		From / To
		☐ Addition ☐ Deletion ☐ Change		From / To
		☐ Addition ☐ Deletion ☐ Change		From / To

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency-Use

Date _____

Patient Initials _____

LABORATORY TESTS

	TEST	DATE: PRE ISOPTIN	During TREATMENT			
HEMATOLOGY	Hemoglobin gm %					
	Hematocrit %					
	RBC x 10^6/cmm					
	WBC x 10^3/cmm					
	Bands %					
	Neutrophils %					
	Lymphocytes %					
	Monocytes %					
	Eosinophils %					
	Basophils %					
	Platelet Estimate (I = Increased, N = Normal, D = Decreased)					

	TEST					
URINALYSIS	Specific Gravity					
	Albumin (0 - 4+) Trace = Tr					
	Glucose (0 - 4+) Trace = Tr					
	Acetone (0 - 4+) Trace = Tr					
	Bile (0 - 4+) Trace = Tr					
	pH					
	Casts/HPF					
	RBC/HPF					
	WBC/HPF					

NOTE. Please circle clinically significant abnormal value and comment as to relationship of each abnormal value to the study drug

_____

_____

_____

INITIALS _____ M D

KNOLL PHARMACEUTICAL COMPANY

ISOPTIN (verapamil) Emergency-Use

Date _____

Patient Initials _____

LABORATORY TESTS
II

TEST	PRE ISOPTIN	During TREATMENT			
DATE					
CHEMISTRIES: Calcium mg %					
Inorganic Phosphorus mg %					
Glucose mg %					
BUN mg %					
Serum Uric Acid mg %					
Tot. Serum Protein gms %					
Serum Albumin gms %					
Cholesterol mg %					
Tot. Bilirubin mg %					
Alkaline Phosphatase Units					
SGOT Units					
LDH Units					
Serum Creatinine mg %					
Creatine Phosphokinase Units					
F.A.N.A. Negative					
Positive					
*Pattern					
Na^+ mEq/L					
K^+ mEq/L					
Cl^- mEq/L					
CO_2 mEq/L					

RIKER PHARMACEUTICAL COMPANY

* Homogeneous = H
Peripheral = P
Speckled = S
Nucleolar = N

NOTE: Please circle clinically significant abnormal values and comment as to relationship of each abnormal value to the study drug

_____

_____

INITIALS _____, M.D.

ISOPTIN (verapamil) Emergency-Use

Date _____

Patient Initials _____

REPORT ON ADVERSE REACTIONS

Check here if no adverse reactions occurred while in the hospital ☐

ONSET			REMISSION			NATURE OF REACTION	DRUG RELATED			SEVERITY		
DATE	TIME		DATE	TIME			YES	NO	UNKNOWN	MILD	MOD	SEVERE
		A.M. P.M.			A.M. P.M.							
		A.M. P.M.			A.M. P.M.							
		A.M. P.M.			A.M. P.M.							

COMMENTS. (Include treatment if any) _____

CLINICAL RESPONSE TO TREATMENT WITH Isoptin.

OVERALL EVALUATION OF EFFICACY.

- Excellent
- Good
- Fair
- Poor
- Condition Worsened

Isoptin

Dosage of Isoptin at time of Discharge

☐☐☐ MG

☐ q8h

☐ q12h

☐ q8h

OVERALL EVALUATION OF SAFETY.

- Adverse reactions were not observed
- Adverse reactions were observed but did not interfere with the clinical response to therapy
- Adverse reactions caused significant interference with the patient's response to therapy
- Therapeutic effects were nullified by the adverse reactions

Isoptin

COMMENTS _____

INITIALS _____, M.D.

BOVEL PHARMACEUTICAL COMPANY